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ENLARGEMENT OF THE INFERIOR OLIVARY NUCLEUS IN ASSOCIATION WITH LESIONS OF THE CENTRAL TEGMENTAL TRACT OR DENTATE NUCLEUS

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INTRODUCTION

THE inferior olivary nucleus (hereafter called "the olive"), in certain pathological conditions, is apt to show a peculiar type of abnormality whose main feature is a conspicuous enlargement. Early references to such "hypertrophy" or "pseudo-hypertrophy" of the olive were made by Oppenheim (1889), Ransohof (1902), Thomas (1903), Marie and Guillain (1903*b*), Klien (1907), Marie and Foix (1913). Interest in this lesion was revived when van Bogaert and Bertrand (1928) drew attention to the constant presence of these olivary changes in palatal myoclonus.

Since the first descriptions, studies of olivary enlargement have progressed along 3 main lines:

(1) The histological features of the olivary changes have been investigated by Lhermitte and Trelles (1933). Alajouanine *et al.* (1935) stressed the importance of vacuolation of the olivary nerve cells. Cases were also reported by Biondi (1934), Marinesco *et al.* (1936), Nicolesco *et al.* (1938), Sittig and Haškovec (1939) and others.

(2) Lesions elsewhere in the brain which were associated with the olivary enlargement were described by Klien, Marie and Foix, van Bogaert and Bertrand, Lhermitte and Trelles. Guillain and Mollaret (1931, 1932), Hillemand *et al.* (1935) also added to our knowledge of associated lesions by their investigations of the lesions associated with palatal myoclonus. It appeared that the most frequently associated structural abnormality was damage either to the central tegmental tract or to the dentate nucleus.

(3) Clinico-pathological correlations (Freeman, 1933; Guillain *et al.*, 1933*b*) showed that palatal myoclonus occurs on the side opposite to the lesions of the olive and central tegmental tract but on the same side as the cerebellar lesions.

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The change in the olive raises several problems which remain unsolved. The exact relationship with palatal myoclonus is far from being clear. The structures which are damaged in the brain-stem or cerebellum are not exactly localized. The nature of the enlargement of the olive and of the cell changes have not received an adequate explanation.

Case Reports

This paper is concerned with 3 cases of olivary enlargement, which have provided an opportunity for studying two problems.

(1) What are the structures, damage to which is associated with the olivary changes?

(2) What is the nature of the chronic enlargement and of the cell changes in the olive?

Case 1.—B. M., a woman of 43, was well until 17.8.46 when, in a cinema, she noticed a bright shape in front of the right eye, which felt hot. Her left eye watered. There was then a feeling of numbness and pins and needles in the fingers of the left hand and later this sensation travelled down her left side to the left leg and up to the left side of her face. She could speak to her husband but her voice was unnatural. She found that her left limbs were paralysed. She was taken to the foyer where she was sick, vomiting three times. She was not giddy. She was taken to Putney Hospital where she had amnesia for forty-eight hours. There, however, she was somnolent but never unconscious. She could reply to simple questions. She was found to have difficulty in articulation, right external rectus palsy and left hemiplegia. After forty-eight hours she became more co-operative but found increased difficulty in articulation and her speech was unintelligible. She had diplopia on looking to either side. Looking to the right images were side by side, to the left one above the other. Left hemiplegia and hemi-anæsthesia were present. The cerebrospinal fluid was normal.

On 2.9.46 nystagmus and inequality of pupils were noted.

On 14.9.46 examination showed bilateral facial weakness, more marked on the right, cerebellar inco-ordination of right arm, weakness and spasticity on left side. Both plantar responses were extensor. Congestion of the left optic disc was noted.

On 24.10.46 she was seen in the outpatient department at the National Hospital. Early papillœdema especially on the left, complete sixth nerve palsy, right lower facial weakness, and left spastic hemiplegia were noted. On the left side cold was felt more intensely and other sensations were diminished.

On admission to the National Hospital under the care of Dr. F. M. R. Walshe (19.11.46) there was marked emotional lability; speech was explosive, staccato and poorly controlled. No aphasia. Intelligence normal. *Cranial nerves:* I. No anosmia. II. V.A.R. 6/9. V.A.L. 6/6. Slight blurring of left disc. III, IV, VI. Partial external rectus palsy on the right; left pupil slightly larger than the right; pupils reacted well; irregular nystagmus to either side and upwards; V. response to cotton-wool, pin-prick, hot and cold impaired over the 3 divisions on the left side. VII. normal. VIII. normal. IX–X. Palate moved in the mid-line. XII. normal. *Motor:* weakness and athetoid movements were seen in the left hand. On both sides there was marked intention tremor and difficulty in finer movements. There was slight weakness of the left leg; co-ordination was fair on the left side but somewhat impaired on the right. *Sensory:* in the left hand gross astereognosis and loss of two point discrimination were noted. In the lower limbs and trunk on the left side there was slight loss to pin-prick, cotton-wool and heat and cold. *Reflexes:* Arm-jerks. R. +, L. ++. Abdominal reflexes

absent. Knee-jerks, R. +, L. ++. Left plantar response was extensor. B.P. 210/105. W.R. negative in blood and C.S.F.

Personal history.—Diphtheria aged 19. Hysterectomy five years ago for menorrhagia. No children or miscarriages.

Family history.—Father died of a stroke aged 50. Mother died of cancer.

On 9.12.46 she had no diplopia and she showed general improvement.

On 16.12.46 at 5.45 a.m., she collapsed with paralysis of left limbs. At 8.15 a.m. deep coma and cyanosis were noted. She died at 8.30 p.m.

Post-mortem was performed fifteen and a half hours after death (P.M.57/46) by Dr. J. G. Greenfield. The body was that of a well-nourished middle-aged woman with an old low mid-line laparotomy scar. No other external signs of disease. Thyroid small. Lungs healthy. Slight mucous bronchitis. Heart: left ventricle thick walled, weight of heart 13 oz. Aorta: slightly atheromatous throughout. Liver normal (congested). Spleen congested, 9½ oz. Kidneys congested. Cortex rather shrunken and capsules stripped with some difficulty. Total weight 9 oz. Stomach and intestines healthy. Except for a small tag of tissue of indeterminate nature attached to the posterior wall of the bladder on its left side there was no trace of the uterus or its appendages.

Histological examination.—In the *kidneys* there was much sclerosis of the glomeruli and many small collections of lymphocytes under the capsule. Bowman's capsules showed fibrous thickening but no crescent formations. No sclerosis of glomerular arterioles was seen. In the *spleen*, in addition to intense congestion, there was hyaline thickening of the intramalpighian arterioles. The *liver* showed no abnormality.

Brain: Skull normally thick. The C.S.F. in the cisterna magna and over the spinal cord was blood stained. There was also slight blood staining of the C.S.F. in the cisterna basalis and the Sylvian fissures. The right vertebral artery was much larger than the left which gave off a very atheromatous posterior inferior cerebellar artery and was continued as a very thin vessel above this. The basilar artery was thin walled but had large plaques of atheroma at its origin and a few farther on in its first half. The pons was swollen and soft. The internal carotid arteries within the skull were only slightly atheromatous but the branches of the right middle cerebral artery were dotted with atheromatous plaques. The anterior cerebral arteries arose normally but did not give rise to a callosal branch. This arose separately near the middle of the anterior communicating artery and passed back as a single branch round the genu and divided about one-third of the way from the genu to the splenium into two lateral branches. It was dotted with atheroma. On opening the right Sylvian fissure the cortex of the insula bulged downwards and on incising here about 2 oz. of blood clot was evacuated. The lateral ventricles contained blood stained fluid and a little clot. In the right cerebral hemisphere a fresh large hæmorrhage extended from the level of the anterior limit of the lateral ventricle to the posterior end of the basal ganglia. In the middle of this extent it was in communication with the right lateral ventricle.

The spinal cord appeared normal.

Histological examination.—Cerebrum: In addition to the large recent right sided cerebral hæmorrhage there was an older one in the right thalamus.

Brain-stem.—Mid-brain: On the right side a region of old necrosis was situated dorsal to the substantia nigra. The necrotic tissue was surrounded by hæmosiderin laden macrophages. Nearby, fresh blood was present, with no cellular reaction around it although the nerve cells contained formol hæmoglobin pigment. It was concluded that this fresh hæmorrhage was part of the terminal cerebral hæmorrhage. On the left side there was extensive gliosis in the region of the red nucleus where very few nerve cells could be seen. *Pons:* On the right side the central tegmental tract, the medial lemniscus and the lateral lemniscus were destroyed (fig. 1A, Plate XLI). The centre of the lesion was of loose texture and some hæmosiderin laden cells were seen there.

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The blood vessels around this destructive lesion were very often cuffed with mononuclear cells. Such appearances were similar to those usually seen where there has previously been a hæmorrhage. On the left side the tegmentum and particularly the central tegmental tract did not show any evidence of damage.

Medulla.—Inferior olive: Celloidin sections stained by hæmatoxylin-van Gieson, phosphotungstic acid hæmatoxylin (Mallory) and iron alum hæmatoxylin (Loyez) were available. Lesions were found (1) in the entire extent of the right olive, (2) in the medial part of the right dorsal accessory olive, (3) in the dorsal part of the left olive (fig. 1B). *Nerve cells:* Most of the nerve cells were abnormal. Many cells showed vacuoles (fig. 1C). These vacuoles were either small and few, small and many or few and very large in any one cell. Many vacuolated cells had an apparent diameter of 70 μ, a few were as large as 100 μ. In the vacuolated cells the nucleus was generally displaced, lying against the cellular membrane. The nucleus was sometimes healthy looking, sometimes the nucleolus was not perfectly round and showed a pale centre. This abnormal appearance of the nucleolus could be observed even when the vacuole in the cytoplasm was of moderate size. Some nerve cells did not show vacuoles. They were frequently of a slightly increased size. No shrunken cells were seen. Non-vacuolated cells lay among vacuolated ones, apparently at random. Many rounded spaces, some optically clear, some faintly brownish with van Gieson's stain were present in the grey portion of the olive. *Astrocytes:* Many astrocytes were hypertrophied, and there was a marked increase of astrocytic fibres. *Microglia:* Some glial stars were seen. *Amiculum:* The amiculum olivæ on each side showed a definite but moderate pallor in myelin preparations with a distribution corresponding to the cellular abnormalities. *The intra-olivary fibres* were not definitely abnormal in preparations stained for myelin. *The inferior cerebellar peduncle* on each side did not show any definite pallor. *Blood vessels:* A slight degree of cuffing of olivary vessels by small round cells was seen.

Cerebellum: In the posterior part of one cerebellar hemisphere a small region showed a loss of Purkinje cells and granular cells together with a conspicuous development of Bergmann astrocytes. Such a lesion was similar to those commonly seen in cases of insufficiency of the cerebellar blood supply.

Case 2.—W. S., a man of 54, was admitted to the National Hospital on 2.3.47 under the care of Dr. Purdon Martin, complaining of headaches, loss of use of legs, and thickness of speech. Since 1940 to 1941 he had complained of weakness of his legs. This weakness had got steadily worse and the legs had also become much thinner.

In November 1946 he had a prostatic operation owing to dribbling incontinence. He had had hæmaturia for eight to nine years. At operation a papilloma was removed from the bladder and histological examination showed it to be benign. Since the middle of 1946 he had had headaches of dull aching type, beginning in the morning on waking and improving during the day. Speech had become thick and slurred and memory poor. In December 1946 he suddenly became dizzy, vomited and had diplopia. Walking had remained poor since then. Bilateral extensor plantar responses were found at that time. B.P. was 250/156. In February 1947 he had a second attack of diplopia.

On admission he was rather euphoric and had a gross slurring dysarthria. No aphasia. He was mentally dull and slow. Incontinence of urine was present. *Cranial nerves:* I, normal. II, discs swollen and pinker than normal. Nipping of veins where crossed by arteries. Numerous hæmorrhages and a macular fan in right eye. No recent hæmorrhages in left eye but white areas of retinal degeneration in both eyes. III, IV, VI, unsustained nystagmoid jerks to right and some limitation of lateral movement in both eyes. Left pupil slightly irregular. V, VII, normal. VIII, normal. IX–X, twitching of palate and pharynx to right, abductor twitching of the

right vocal cord at a frequency of about 140 per minute. XI, XII, normal. *Motor:* arms, very slight ataxia. No wasting. Legs, wasting of calf and quadriceps, hamstrings and glutei were present and more marked in left leg with gross ataxia. *Gait:* he walked only with assistance and gait was very ataxic. *Sensation:* some defect of joint sense was found in the right hand. Legs: vibration sense was diminished in both shins; gross loss of joint sense was present in toes and to a less degree in ankles. There was marked hypoalgesia in the sacral region. *Reflexes:* arm-jerks brisker on the right. Abdominal reflexes present on both sides. Knee-jerks brisker on the right. Ankle-jerks absent on both sides. Both plantar responses were extensor. B.P. 260/170.

14.3.47: Lumbar puncture gave cerebrospinal fluid under a pressure of 160 mm. Cells 4 per c.mm. Total protein 80 mg. per cent. Lange: 0000121100. W.R. negative. 28.3.47: Blood urea normal. He then developed severe urinary infection with progressive increase of blood urea. During the last week of his life he was very drowsy and developed jaundice. Numerous subcuticular hæmorrhages were seen on the face. 27.4.47: Blood urea 216 mg. per cent.

Post-mortem examination was performed twenty-two hours after death (P.M. 32/1947) by Dr. J. G. Greenfield. The body was that of a thin middle-aged man with fairly severe jaundice. No other evidence of disease on external examination except scar of suprapubic cystotomy. Thyroid fairly large, firm and yellow. Lungs: some œdema of all lobes but no obvious consolidation or abscess formation. Adhesions to chest wall. Several rather large glands were present at the root and in the retro- and subtracheal part of the mediastinum. Heart 1 lb. 4 oz. Left ventricle thick walled. Aorta showed patchy atheroma, not severe, and there was no thickening and very little stretching of the aortic valve cusps. Liver rather yellow, smooth, not enlarged. Gall-bladder distended but emptied easily in duodenum where some bile was already present. Stomach and duodenum healthy. Intestines normal. Spleen 8 oz. dark and firm, rather enlarged. Kidneys large, 8 oz. each with mottled pale cortex. Capsules stripped leaving a smooth surface. Bladder small and thick walled. Some prostatic tissue still present but not unduly adherent to surrounding tissues.

Histological examination.—The *liver* showed fairly large irregular areas of degeneration and necrosis of liver cells, associated with an excess of lymphocytes in the portal tracts where there was also a proliferation of connective tissue. The degeneration of liver cells appeared to be chiefly periportal but was rather irregular. The *spleen* was intensely congested and also showed some hyaline thickening of the walls of the malpighian arterioles. The *lungs* showed slight patchy bronchopneumonia and inflammation limited to the immediate surroundings of the bronchioles, with considerable catarrhal exudate into the other alveoli in the neighbourhood and in some places œdematous exudate.

Spinal cord normal to the naked eye but, histologically, Weigert-Pal preparations showed pallor of the medial portions of fasciculus gracilis on each side. At the midthoracic level only the medial halves of the dorsal white columns were affected and these were not completely demyelinated. There was a constriction of the lumbar canal at the junction of the fourth and the fifth vertebral bodies by projection of disc tissue into the canal especially on the right side. The space between the vertebral bodies, which were separated except at their margin, was occupied by soft friable fibro-cartilagenous tissue which could easily be picked out of the cavity. There was heavy bossing over the junction of the vertebral bodies on the right anterior aspect.

Brain: There was in the cerebrum a small slit due to hæmorrhage in the outer part of the right putamen. Another hæmorrhage undercut the cortex at the bottom of a sulcus in the right occipital region. There was no noticeable evidence of softening or other hæmorrhage in the cerebrum. There was rather more tonsillar herniation on

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the right side than on the left. In the naked-eye examination of the brain-stem the only lesion in the pons and mid-brain was a small central softening in the mid-line of the pons, just posterior to the medial lemniscus, at about the mid-level of the pons. (This lesion was not visible in the microscopical sections which were available.) In the cerebellum there was brownish softening involving all the region of the right dentate nucleus. This was associated with a very dilated vein running posteriorly just below the nucleus, and dilatation of the vessels in the white matter almost everywhere in the right hemisphere (fig. 2A). The condition appeared to be a hæmorrhage arising from an angioma.

Histological examination.—Brain-stem and cerebellum: Celloidin sections stained with thionin (Nissl), hæmatoxylin-van Gieson, phosphotungstic acid hæmatoxylin (Mallory), iron alum hæmatoxylin (Loyez), ammoniacal silver (modified Bielschowsky) were available. *Cerebellum:* Extensive hæmorrhage involved the cerebellar nuclei (fastigial, intermediate and dentatus) on the right side and extended to the white matter of the nodulus and the uvula. The hæmorrhagic lesions were of two ages: (1) Some were rather old and contained very numerous hæmosiderin laden cells. (2) Some were recent and contained free blood. The lesions involving the cerebellar nuclei belonged mainly to (1). Among the infiltrated tissue some of the nerve cells appeared to be relatively spared. In the cortex of the vermis and right cerebellar hemisphere, particularly in the posterior aspect, many of the Purkinje cells were not present. Astrocytes were present in increased number in the Purkinje cell layer and numerous astrocytic processes were seen extending across the molecular layer.

A very large blood vessel was present in the cerebellum separating the nodulus from the uvula and, farther laterally, it lay approximately between the tonsil and the lobulus gracilis inferiorly and the white substance of the hemisphere superiorly. Throughout the cerebellar white matter of this region very numerous blood vessels were seen, some capillaries being calcified, some being surrounded by free blood. In the tissue infiltrated by blood several vessels appeared to be occluded by thrombus. On the postero-inferior aspect of the cerebellum unusually large blood vessels were present. In sections stained for myelin the right superior cerebellar peduncle showed a pallor most conspicuous in its medial half. *Mid-brain:* Pallor was seen in the region of the left red nucleus. Throughout the left superior cerebellar peduncle and left red nucleus area lesions of ischæmic type were seen. In the region of the right red nucleus a small focus of ischæmic type was also present. *Pons:* The tegmentum of the pons did not show any abnormality. In the central tegmental tract several thick fibrous-walled arterioles were seen but the myelin had a healthy appearance. In the pons proper several fairly recent small foci of necrosis were seen. *Medulla:* To the naked eye, the bulk of the left inferior olive appeared to be conspicuously increased (fig. 2B). Histological examination revealed that lesions were present: (1) throughout the entire left inferior olive, more marked in the ventral lamina; (2) throughout the right inferior olive but much less severe.[1] *Nerve cells:* there was a marked absence of nerve cells from the ventral lamina of the left olive. Amongst the nerve cells which were present in each olive, vacuolated nerve cells were not numerous (fig. 2C), and were found as often in the right olive as in the left. No vacuolated cell had a diameter exceeding 50 μ. Non-vacuolated cells of slightly increased or normal size were seen among vacuolated ones, with an apparently random distribution. With silver impregnation (modified Bielschowsky) some nerve cells showed a moderate but definite enlargement of the cell body (fig. 2D), and a very definite enlargement of the cell processes (fig. 2E). Such abnormal cells were mainly present in the enlarged olive but some of them were also found in the less affected (right) olive. *Astrocytes:* The number and size of

[1]Figs. 1, 3 (a) and (b), page 19, in "Neuropathology," Greenfield, 1958, are from this case.

astrocytes were increased. Gemistocytic astrocytes were present as well as some binucleated ones. Dense gliosis was seen in the ventral lamina of the left olive. *Microglia:* There was a noticeable infiltration of the olivary grey matter by microglial cells. *Vessels:* Occasionally a slight degree of cuffing with small round cells was seen. *Amiculum:* In sections stained for myelin a very slight pallor of the left amiculum was seen. *Intra-olivary fibres:* A very marked pallor of the intra-olivary fibres was seen in the hilum of the left olive and could be followed across to the right side of the medulla towards and into the right inferior cerebellar peduncle. Here, however, lesions of vascular origin were also present. The amiculum and intra-olivary fibres on the right side appeared normal in myelin preparations and the left inferior cerebellar peduncle appeared normal in sections stained by Loyez and Mallory's techniques. The nucleus ambiguus on each side appeared to be normal.

Case 3.—J. H., was a woman of 29 whose brain was received from an outside hospital. In 1924, aged 11 years, she had severe morning vomiting and headache lasting two hours every morning for a week with about a week's interval between attacks. After about three to four weeks, on waking one morning, she found that she was dragging her left foot and falling to the left. She also vomited. She was said at that time to have a hæmorrhage behind the left eye. She recovered in three to four weeks. Since 1924 she remained well till 1939 when she began to fall again. At this time she complained of slight deafness and bilateral tinnitus. She then began to put on weight and became slow in her speech reactions. In December 1939 some difficulty in holding her urine was noted. In January 1940 she fell on going upstairs. Immediately afterwards she found that she could not see properly. In February 1941 she was admitted to Guildford Hospital. She was dull mentally; left eye remained in inner canthus from the beginning of this attack and she had diplopia. She had difficulty in speaking and in swallowing especially fluids. She had lost the sense of taste for tea. Difficulty in holding water was noted. On lumbar puncture the cerebrospinal fluid was clear and faintly yellow, W.R. negative, protein 30 mg. per 100 ml., cells 6 r.b.c. and 16 lymphocytes per c.mm. She was discharged home in May 1941. She became brighter mentally. The left side of her face became drawn up. On 3 occasions she suddenly went stiff all over and fell to the ground. On one occasion she was incontinent.

Family history.—Father died of cerebral hæmorrhage and tabes dorsalis.

9.6.42 admitted to the National Hospital, Queen Square, under the care of Dr. F. M. R. Walshe.

On examination (9.6.42) she was obese, very euphoric with gross defect in memory. Her head was large. *Cranial nerves:* I, normal. II, no papillœdema. III, IV, VI, left eye fixed in inner canthus. Fine rapid horizontal nystagmus of right eye looking to the right, less rapid to the left, and in the left eye on deviation to the right. No nystagmus on looking upwards. V, left masseter weak. Diminution of sensation over right trigeminal area. Right and left corneal reflexes diminished. VII, weakness of left side of the face with contractures. VIII, normal. IX, X, paresis of soft palate on left side. Twitching of the soft palate to right, left vocal cord fixed. XII, atrophy and weakness of left side of the tongue. *Motor:* spasticity of left arm and wasting of small muscles of left hand were present. There was gross inco-ordination in both arms especially the left one. Left leg was more spastic than right, gross cerebellar type of ataxia was noted in both legs, more marked on the right. *Reflexes:* Arm-jerks and abdominal reflexes absent, knee and ankle jerks present. Plantars were flexor. *Sensations* of pin-prick and temperature were diminished on right side of the body. C.S.F. was normal. W.R. negative. She was discharged on 14.7.42. She died on 19.8.42.

The brain was received from Leavesden Emergency Hospital (P.M. 13/42).

Post-mortem examination of the brain (Dr. J. G. Greenfield).—There was gross

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bilateral hydrocephalus affecting all the ventricles, with dilatation of the iter of Sylvius, fourth ventricle and of both foramina of Luschka which were about 1 cm. in diameter. The right cerebellar hemisphere was thinner from above down than the left and there was thickened rather opaque arachnoid over the inferior surface of this lobe and of the vermis. There was slight granularity of the floor of the fourth ventricle and of the walls of the lateral ventricles. The septum pellucidum was widely fenestrated so that only a few shreds ran from above downwards. The posterior ends of the choroidal fissures were opened up and the ventricles closed here by arachnoid only, over a circular area of about 1·5 cm., but there was no bulging of this arachnoid. *Brain-stem:* Sections from the upper part of the pons to the decussation of the pyramids could be examined. Sections were stained with thionin (Nissl), hæmatoxylin-van Gieson, phosphotungstic acid hæmatoxylin (Mallory), iron alum hæmatoxylin (Loyez), ammoniacal silver (Gros-Bielschowsky) counterstained with neutral red were available. A syrinx was situated in the left tegmentum of the pons (fig. 3A) and medulla (fig. 3B) as a transverse cavity which reached but did not pass the median raphe. In the pons the cavity involved the region of the central tegmental tract, medial lemniscus and trapezoid body. In the superior part of the pons the cavity tapered laterally and involved the more medial part of the superior cerebellar peduncle. Caudally the syrinx extended into the medulla, following the dorsal aspect of the inferior olive. There the cavity had considerably narrowed and consisted of a narrow slit extending from the median raphe anterolaterally as far as a parasagittal plane which passed through the dorsal motor nucleus of the tenth cranial nerve. The cavity was there surrounded by heavy gliosis. Below the inferior olive the syrinx involved bilaterally the inferior part of the medulla oblongata. At the level of the decussation of the pyramids a transverse slit extended across the grey matter of the posterior column on the right and a small cavity was found in the left spinal root of the fifth nerve. Below the decussation the cavity extended bilaterally into both spinal roots of the fifth nerve, arching behind the central canal. To the naked eye the left inferior olive appeared to be much swollen. Its dorsal aspect was lying close to the floor of the fourth ventricle due to collapse of the syrinx dorsal to the olive. Olivary lesions were found (1) in the entire extent of the left inferior olive, more marked in the ventral lamina; (2) in the left medial accessory olive; (3) in the medial part of the ventral lamina of the right inferior olive where a few cells appeared abnormal.

Nerve cells: There were only about 20 per cent. as many nerve cells in the convolution on the left side as on the right. The absence of nerve cells was, however, most striking in the ventral lamina. The nerve cells were pale with Nissl and neutral red stains (fig. 3C). A few appeared to be shrunken. Very few showed vacuolar changes, and hypertrophy of nerve cells was a rare feature. When vacuolation was present the size of the cells was only slightly increased. Instances in which the longer diameter of the cell reached 50 μ were found to be exceptional. Rounded spaces, optically clear or faintly stained, in the grey lamina were also exceedingly rare.

Astrocytes: The number of astrocytic nuclei and astrocytic fibres was markedly increased in the left inferior olive. Microglial nuclei were also present in increased number. Glial stars were seen. In sections stained for myelin there was marked pallor of the amiculum and hilum of the left inferior olive. Only a few olivo-cerebellar fibres could be seen and there was conspicuous pallor of the right inferior cerebellar peduncle. The olivo-cerebellar fibres, from the right inferior olive, appeared to be normal in the region where they crossed the left inferior olive on their way to the left inferior cerebellar peduncle. The left external arcuate fibres showed marked pallor. The ventral arcuate nuclei appeared to be normal. The right nucleus ambiguus was of normal appearance; the left could not be found. The right medial lemniscus was markedly pale, in sections stained for myelin, throughout the medulla oblongata.

Cerebellum: There was slight pallor of myelin staining round the dentate nucleus on the right side but the fibres in the hilum appeared normal. In the cerebellar cortex there was no obvious loss of nerve cells but a large number of torpedoes were present on the axons of Purkinje cells in the right half of the cerebellum. There were only a few torpedoes in the left hemisphere. There was a remarkable aggregation of swollen axons and globular argentophil masses under the wall of the fourth ventricle internal to the dentate nucleus on both sides and a smaller number of rounded argentophil masses in the walls of the lateral ventricle. A large number of similar bodies was seen in the right eighth nerve at its junction with the medulla oblongata.

Summary of Histological Findings

The lesions observed in our cases were similar to those reported in the literature as "hypertrophy" or "pseudo-hypertrophy" of the inferior olive.

(*a*) The changes in the olive consisted of: (1) an increase in size of the inferior olivary nucleus; (2) the presence of numerous and sometimes very big vacuoles in the nerve cells. In some places the grey lamina was riddled with multiple round clear spaces, many of which were probably vacuoles ("aspect fenêtre," Alajouanine *et al.*). Non-vacuolated cells were also present. Some were slightly enlarged, some appeared to be of normal size. Very few cells were shrunken. In some cases and especially in the ventral lamina of the olive the absence of nerve cells was striking. In one case a silver impregnation (modified Bielschowsky) of the nerve cells was available. Fixed, unstained material from the other cases was not available. This silver impregnation showed hypertrophy of cell bodies and cell processes similar to that first described by Lhermitte and Trelles. (3) Gliosis and microglial reaction. (4) In myelin preparations pallor of various intensity of the amiculum olivæ and of the intra-olivary fibres.

In every case the lesions were bilateral but the enlargement of the olive appeared to be unilateral. In the less affected olive the lesions were of very mild intensity and mainly consisted of scattered vacuolated cells.

(*b*) The lesions in the brain-stem or the cerebellum were similar in situation to those in the cases previously reported.

(1) In 2 cases (Cases 1 and 3) the lesion involved the tegmentum of the pons, especially the central tegmental tract. In Case 1 the lesion was an old hæmorrhage. Most of the cases so far reported have also been of vascular origin either hæmorrhages or softenings. In Case 3 the lesion which involved the central tegmental tract was a syrinx which involved the medulla oblongata and the pons. So far as we know no other case of enlargement of the inferior olive associated with a syrinx has been reported. We have only found one relevant case, that of Schlesinger quoted by Jonesco-Sisesti (1932) in which palatal myoclonus was observed during the course of a syringobulbia, thus strongly suggesting the presence of an enlarged olive. Examination of the medulla was not reported. In both cases of involvement of the central tegmental tract the enlarged olive was on the same side as the lesion of the tegmentum.

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(2) In one case (Case 2) the lesion involved the dentate nucleus and was a hæmorrhage from an angiomatous malformation. The enlarged olive was on the side opposite to the damaged dentate nucleus.

The Lesions in the Brain-stem and Cerebellum

The ætiology of enlargement of the olive was ascribed by earlier workers to various factors. Marie and Guillain (1930*b*) suggested the possibility of a vascular origin of the olivary lesions. Marie and Foix (1913) felt that the association of syphilitic inflammatory lesions with damage to the central tegmental tract played a role in the genesis of the olivary changes. A possible local action of *Treponema pallidum* was suggested by Lhermitte and Trelles (1933). Since then the evidence has suggested that the causes of the olivary changes were lesions involving other parts of the nervous system, especially the central tegmental tract or the region of the dentate nucleus.

Lesions of the Central Tegmental Tract

The association of lesions in the central tegmental tract and in the inferior olive was first mentioned by Ransohof (1902) and Thomas (1903) and has subsequently been found by many authors (*vide infra*). The central tegmental tract is a composite bundle and from numerous anatomical researches divergent conceptions have emerged. That the fibres arise in one or more of the red nucleus, peri-aqueductal grey substance, cerebellar nuclei, corpus striatum or thalamus has been described by some and denied by others. Thorough reviews and personal contributions are to be found in Mettler (1944), Verhaart (1949, 1956, 1958), Cardona and Macchi (1950) and Bebin (1956). From our present knowledge it appears that, in man, the central tegmental tract is composed, mostly, of fibres going to the inferior olive, and that these fibres arise in the upper parts of the brain-stem, particularly in the red nucleus and its vicinity. It is possible that crossed fibres from the superior cerebellar peduncle join the tract and reach the inferior olive. On many points, however, our present knowledge must be considered as provisional and conclusions about the consequences of lesions of the tract must be regarded with caution.

The lesions of the central tegmental tract which are associated with olivary enlargement are most frequently situated in the tegmentum of the pons, at a level where all or most of the fibres to the inferior olive have already entered the tract. Such pontine lesions generally involve the whole tract. Therefore they give no clue as to whether damage to a particular group of fibres is concerned with olivary enlargement. In a few cases (Marie and Guillain, 1903*a;* Souques *et al.*, 1930; Jakob and Montanaro, 1938; Guillain *et al.*, 1938) lesions situated rostral to the decussation of the superior cerebellar peduncle were associated with pallor, in myelin preparations, of the amiculum olivæ, with or without cell loss but without enlargement of the olivary nucleus. It is therefore possible that lesions

of particular components of the central tegmental tract are responsible for the olivary enlargement and, moreover, that these components entered the tract caudal to the decussation of the superior cerebellar peduncle. The hypothesis was put forward by Trelles (1944) that dentato-olivary fibres, reaching the brain-stem via the superior cerebellar peduncle, were the particular group of fibres, damage to which is associated with olivary enlargement. Such fibres had been stated to exist in man (Jakob, 1942). This appeared to provide a satisfactory explanation for the crossed lesions in the olive following damage to the dentate nucleus and for the ipsilateral olivary changes after damage to the central tegmental tract. It must, however, be recognized that other findings do not appear to support this view. One would expect to find enlargement of the contralateral olive after lesions of the superior cerebellar peduncle, but olivary enlargement [apparently] does not occur in this condition. Guillain *et al.* (1933*b*) have reported a case in which a lesion of the right superior cerebellar peduncle was associated with damage to the right central tegmental tract and in this case only the right olive showed enlargement. Very slight changes which were similar to those usually observed after damage to the right central tegmental tract were seen in the left olive. Moreover, it must be emphasized that, in cases where enlargement of the olive was associated with lesions of the dentate nucleus, the central tegmental tract was not found to be abnormal by most workers (van Bogaert and Bertrand, 1928; Garcin *et al.*, 1933; Biondi, 1934; Lhermitte *et al.*, 1935*b;* de Savitsch and Ley, 1937; Lhermitte and Drouzon, 1937; Nicolesco *et al.*, 1938; Sittig and Haškovec, 1939; Murphy and Langworthy, 1939; Freeman and Jaffe, 1941; Guillain *et al.*, 1943; Nathanson, 1956). Similarly in our Case 2 no evidence of abnormal fibres was found in the central tegmental tract. It can thus be concluded that: (1) When the lesion is situated in the pons the question of damage to dentato-olivary fibres as a cause of the olivary enlargement cannot be answered with certainty; (2) when the lesion involves the dentate nucleus evidence of damage to dentato-olivary fibres in the central tegmental tract is more often lacking.

Admittedly, in long-standing lesions, degenerated fibres may be difficult to demonstrate; the only evidence of abnormality in a tract from which a part has disappeared may be a slight shrinkage of this tract. In a poorly defined tract, such as the central tegmental tract, in which dentato-olivary fibres (Jakob, 1942) would be but a part, such a shrinkage would be particularly difficult to recognize. In addition it must be pointed out that most of the pathological studies have been carried out with stains for normal myelin only. It would be interesting to investigate future cases with stains for degenerating myelin and nerve fibres. At present it may be concluded that insufficient evidence is available to ascribe to a particular group of fibres in the central tegmental tract a specific role in olivary enlargement.

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Lesions of the Dentate Nucleus

It is known that a lesion of the dentate nucleus may be associated with enlargement of the contralateral olive. The anatomical basis for this finding must now be considered. The possible role of damage to dentato-olivary fibres entering the central tegmental tract via the superior cerebellar peduncle has just been considered. The possibility of dentato-olivary connexions via the inferior cerebellar peduncle, which appear to be unimportant in the cat (Jansen and Jansen, 1955) cannot be excluded in man because of our lack of anatomical knowledge on this subject (Jansen, 1954). It should be noted, however, that there is no evidence that lesions in the inferior cerebellar peduncle are concerned with olivary enlargement.

A similar lack of anatomical knowledge makes it difficult to reach any conclusion about the role of damage to olivo-cerebellar connexions. Fibres going from the olive to the cerebellar cortex are well known but the existence of olivo-dentate fibres in man is yet unproved. Such connexions have been described in the cat and the rabbit (Brodal, 1954) but in human material (Henschen, 1907; Holmes and Stewart, 1908; Pines and Liberson, 1934) the pathological lesions were not confined to a particular structure and it would therefore appear very difficult to draw firm conclusions about anatomical connexions. Lesions of the dentate nucleus, including as a rule some of the adjacent white matter, may involve olivo-cerebellar (cortical) fibres as they pass close to the dentate nucleus. The role of such involvement would appear to be supported by those cases of olivary enlargement in which there was a dentate lesion and pallor of the inferior cerebellar peduncle in myelin stains, but no demonstrable change in the central tegmental tract (Lhermitte *et al.*, 1935*b*; Sittig and Haškovec, Murray and Langworthy, Guillian *et al.*, 1943; Nathanson, our Case 2). Such a view, however, does not receive support, as pointed out by Trelles, from the many cases in which the olivo-cerebellar fibres were destroyed in the lateral part of the medulla oblongata but the olives were not enlarged. We have not found any mention of olivary enlargement in cases of posterior inferior cerebellar artery occlusion, although admittedly in this condition the lesion may not always involve all the olivo-cerebellar fibres and the fact that some of the fibres are spared may possibly be of significance. Neither did we find olivary enlargement in cases of syringobulbia where the syrinx had interrupted the olivo-cerebellar fibres. In this condition Jonesco-Sisesti (1932) sometimes found pallor of the peri- and intra-olivary fibres but apparently no olivary enlargement. The olive was of normal size in a case of Greenfield's in which the syrinx extended across the entire region where the olivo-cerebellar (cortical) fibres were thought to have passed. Damage to the distal part of the olivo-cerebellar (cortical) fibres does not appear to give rise to olivary enlargement. In such a condition Holmes and Stewart mentioned swelling and vacuolation of the olivary cells but no enlargement

of the olivary nucleus. Finally the most likely hypothesis relating damage to the dentate nucleus with olivary enlargement appears to be Trelles', namely that there is involvement of those dentato-olivary fibres which enter the central tegmental tract. Future pathological studies should be carried out to find evidence either to support or to disprove this hypothesis.

Some facts which stand apart from the general rules must, however, be kept in mind. Lesions of the central tegmental tract are not always associated with enlargement of the olive (Marie and Foix, 1913; Lhermitte, 1913; Freeman and Jaffe, 1941). In the kitten olivary cell changes are usually quite noticeable after damage to the brain-stem but they may be absent after apparently similar lesions (Torvik, 1956). Also olivary enlargement has been reported in the absence of lesions in the brain-stem and cerebellum (Marie and Guillain, 1903*b*; Guillain *et al.*, 1933*b*). There have been cases where enlargement of the olive was associated with lesions of the dentate nucleus without any visible abnormality in the central tegmental tract or inferior cerebellar peduncle. The two pathological processes were then assumed to be independent of each other (Garcin *et al.*, 1933; Biondi, 1934). Such findings emphasize the possible significance of local factors in the olive, as suggested by early authors. It is also possible that local factors play a role in the severity and extent of the changes occurring in the olives in association with lesions involving the central tegmental tract or the dentate nucleus.

The Nature of the Histological Changes in the Olive

Consideration of the nature of the histological changes which occur in the enlarged olive raises several problems, among which the following will be considered: (1) the changes in the nerve cells; (2) the increase in size of the olivary nucleus.

(1) *Changes in the nerve cells.*—These consisted of (*a*) increase in size; (*b*) disappearance.

(*a*) *Increase in size:* Some cell bodies were slightly enlarged and, in the one case in which it was investigated, the processes were also enlarged. Some cell bodies were greatly enlarged, with vacuolation of the cytoplasm. Vacuolation is a pathological process by no means limited to the olive and it can apparently occur in a variety of conditions. When associated with damage to the central tegmental tract vacuolation in the olives would, however, appear to result from an unusual disorder. It is now generally agreed that only descending fibres enter the central tegmental tract (Verhaart, 1949; Bebin, 1956); olivary cell changes are thus the consequence of lesions involving afferent neurones, i.e. vacuolation is a consequence of transsynaptic degeneration. Experimental studies have yielded comparable data: in the cat after removal of an eye vacuolated cells in the lateral geniculate body were seen by Cook *et al.* (1951); in kittens after damage to the brain-stem small vacuoles were sometimes observed in olivary cells (Torvik, 1956); in completely deafferented spinal anterior

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horn cells vacuolation was also observed by Tower (1937). Isolation of nerve cells from their afferent fibres would thus appear to provide conditions favourable to the formation of vacuoles. Little is known about the mechanism either of transsynaptic degeneration or formation of vacuoles. Whatever the exact disturbance, vacuolation implies a disorder of the metabolic exchanges between the cell and its environment. It may be supposed that, in transsynaptic degeneration, the boutons terminaux which coat the cell body undergo marked changes and eventually disappear, leaving a "naked" cell, the exchanges of which must be profoundly disturbed. It would not be surprising to find vacuoles in such affected cells. Transsynaptic degeneration is not however always accompanied by vacuolation. In the cat transsynaptic degeneration in the lateral geniculate body was primarily marked by decrease in size of the cell body, nucleus and nucleolus (Cook *et al.*, 1951) and in the inferior olive of kittens, the main changes observed by Torvik consisted of shrinkage, nuclear pyknosis and karyorrhexis. In the human lateral geniculate body, cells undergo primarily shrinkage (Greenfield *et al.*, 1958). Swollen cells but no vacuolation were found by Penman and Smith (1950) in the sensory nucleus of the fifth cranial nerve fourteen weeks after alcohol injection of a trigeminal ganglion. It is thus still necessary to ask why, in the human inferior olive, does transsynaptic degeneration give rise so constantly to such prominent vacuoles? It is possible that the very peculiar cellular and afferent pattern of the human olive (Scheibel *et al.*, 1955, 1956) has some bearing on this peculiar consequence of transsynaptic degeneration.

(2) *Increase in size of the olivary nucleus.*—The actual increase in size of the olivary nucleus is often of moderate degree; for which reason Marie and Foix (1913) favoured the name of "pseudo-hypertrophy" although they admitted that there was a slight increase in volume of the grey substance. Previously Thomas (1903) had stressed the point that, in fact, there was a decrease in number and size of cells and had stated that hypertrophy only of ground substance had occurred. Lhermitte and Trelles stressed the presence of enlargement of the nerve cell bodies and their processes and favoured the name of "hypertrophy." Eventually Lhermitte *et al.* (1935*a*) drew attention to the fact that in some cases there might be a "pseudo-hypertrophy" due to pallor of the amiculum and intra-olivary fibres, which produced an apparent increase of size of the grey lamina. In such cases enlargement of cells was lacking. It is true that pallor of myelin around and within the olive may result in an apparent enlargement of the grey lamina or may make a true enlargement of the grey portion of the olive appear greater than it is. Nevertheless in many cases an actual enlargement of the olivary nucleus does take place.

In the 3 cases it is obvious from the illustrations (figs. 1B, 2B and 3B) that one olive is larger than the other. It is not, however, obvious whether the enlargement is partly or wholly in the grey lamina, the intra-olivary

region and/or the amiculum, and how the size of the olives in our cases compares with the normal.

Magnified ($\times 21$) projections of the olives in figs. 1B, 2B and 3B and of a pair of olives from a "normal" adult were accordingly made on cardboard of uniform thickness. The various regions were then cut out and weighed. Since the cardboard was of uniform thickness the weight of each piece was proportional to its area. The weight of 400 sq. cm. of the cardboard was 12·82 grammes, from which data it was possible to calculate the actual areas of the pieces. The results are shown in Table I.

TABLE I.—MEASUREMENTS OF MAGNIFIED OLIVES AND THEIR COMPONENTS

	Case 1		*Case* 2		*Case* 3		*Normal case*	
Areas in sq. cm.	*Smaller olive*	*Larger olive*	*Smaller olive*	*Larger olive*	*Smaller olive*	*Larger olive*	*One olive*	*Other olive*
Grey lamina	54·61	85·80	39·00	53·04	39·00	68·64	38·69	37·13
Amiculum	43·68	54·61	35·88	42·12	73·33	70·23	37·76	33·08
Intra olivary region	35·88	67·08	34·33	53·04	57·73	99·84	30·58	40·88
Total area of olive	139·17	207·49	109·21	148·20	170·06	238·71	107·03	111·09
Number of major convolutions	16	16	16	15	17	16	16	16
Length of the grey lamina in cm.	67	94	55	72	70	104	70	63·5

From these results it appears that in each of the cases the grey and white matter were increased in size in the principally affected olive as compared with the olive on the other side and that all the olives except for the smaller olive in Case 2, were larger than "normal." It must be admitted that our measurements concerned only transverse (approximately horizontal) sections of the olives and that we have no measurements of the olives in longitudinal (vertical or parasagittal) sections. The material available did not permit us to make measurements in this plane, but we have no reason to believe that the relative increase in size of one olive in the transverse plane was compensated for by shrinkage in the longitudinal plane.

The question then arose as to what changes could account for the increases in size.

Increase in size of the grey matter.—Many nerve cells undoubtedly were greatly enlarged, due in our cases to the presence of vacuoles, and to enlargement of processes in the one case in which it was investigated. Non-vacuolated cells were frequently of slightly increased size. Such increase in cell volume might explain, at least in part, the increase in size of the inferior olive. It must be noticed, however, that loss of cells was

observed concomitantly with vacuolation or enlargement and it must be stressed that in Case 3, the case of longest duration, when vacuolated cells were few and the absence of cells was very marked, the enlargement of the grey lamina of the larger olive was still considerable when compared with the normal. Thus it would appear that enlargement of nerve cells cannot provide a complete explanation for the increase in size of the grey portion of the olive. Increase in size and in number of astrocytes and increase in number of microglia was also present and must be taken into account where enlargement of the olive is considered. It may be remarked, however, that such glial changes occur in the grey matter of other parts of the nervous system in other disease processes, and that they do not appear to cause an increase of volume of the nervous tissue. Finally evidence for or against an increase in the space occupied by the ground substance was impossible to obtain in our experience.

Increase in size of the white matter.—The increase in size of the amiculum was of moderate amount in Cases 1 and 2. In Case 3 the bulk of the amiculum was increased, but equally on each side, a fact possibly related to the presence of a syrinx close to the dorsal aspect of the larger olive.

The increase in size of the white matter in the sac of the olive in our cases appeared to be the main factor of the increased size of the olive. In Case 3, the cross-sectional area in the enlarged olive was almost twice that in the opposite one.

Increase in size of white matter may be due to (1) *neoplasia*, of which there was no evidence. (2) "*Œdema.*" We have no figures for the dry and wet weights, volume or chemical nature of any fluid, to compare with those estimated for cerebral œdema. The histological appearances of the white matter were not those usually seen in œdema of short duration. The myelinated nerve fibres were less closely packed in the larger as compared with the smaller olive but there were no signs of active degeneration of myelin or of fibres, no noticeable reaction on the part of the astrocytes. Since the enlargement of the white matter in our cases was present four months after the onset of symptoms in one case, and at least one year in another case, it could be suggested that the changes were those of œdema of long duration. We can only say that in two personal unpublished cases, where the evidence was in favour of œdema of long duration at the periphery of meningiomata, the changes in the white matter were those of replacement of white matter by fluid-filled cavities. This was not present in the enlarged olivary white matter. The evidence, such as it is, does not support a diagnosis of œdema. (3) *Ischæmic necrosis* of short duration. The histological appearances were not those of this condition. (4) *Increase of the ground substance* of the white matter, neither for nor against which did we find evidence.

Having thus excluded all the possibilities which immediately presented

themselves, we cast about for some other explanation for the increase in size of either the grey matter or of the white matter in the sac of the olive.

We were not aware of any other nucleus, in the brain or cord, which became similarly enlarged, in association with damage to its afferent nerve fibres (the central tegmental tract). We therefore wondered what anatomical peculiarities existed in the olives. The most prominent were (1) the peculiar and, apart from the dentate nuclei, unique folding of the grey lamina of each olive, in which the lamina is convoluted and forms a kind of open-mouthed sac or bag. (2) The dense meshwork of astrocytic processes which bind together the grey lamina. (3) The medusa-like processes of many of the nerve cells of the olives.

In view of the peculiarities of the grey lamina we re-examined this layer of the olives. We found that the number and pattern of the major convolutions of the enlarged olive, in each of our 3 cases, was not markedly different from that of the other olive or from the normal. We found that the length of the grey lamina, as measured along the middle of its width, was considerably greater, in each case, in the larger olive than in the other olive, being in the ratio of 1·4, 1·3 and 1·5 to 1. In each case therefore the two olives were similar in pattern, but one had a greater length of grey lamina than the other. This could only mean that the length of each side of each fold became longer, e.g. ⊃ became ⊃ and ⊂⊃ became ⊂⊃. The larger figure inevitably contained a greater area within its sac. It seemed to us therefore that the increased size of the contents of the olivary sac could be, at least in part, accounted for by the increase in length of the grey lamina. The similar convolutional pattern of the two olives was evidence against the enlargement of the olive being due to a primary swelling of the contents of the olivary sac. The wider separation of the myelinated nerve fibres within the larger olive could be explained as a passive separation of the nerve fibres due to the greater length of the containing wall.

We had noted, as shown in fig. 1B, that the grey lamina of the larger olive was not only longer than that of the smaller olive but that it was also, for the most part, wider. Our measurements in Table I enabled us to check this mathematically. In each case we knew the areas and the lengths of the grey laminæ. The *average* widths must equal areas ÷ lengths. The results of this calculation showed that the *average* width of the grey lamina of the larger olive was greater in each case than that of the smaller olive, although the increase was small (Case 1, 1·12:1; Case 2, 1·04:1; Case 3, 1·2:1). The average width of the grey lamina of the larger olive as compared to those of the normal case was Case 1, 1·6:1; Case 2, 1·3:1; Case 3, 1·2:1.

It now remained to attempt to explain the increased length and width of the grey lamina. This has been considered above and it has been con-

cluded that enlargement of the nerve cells cannot provide a complete explanation for this increase in size of the grey lamina. We do, however, know that such an enlargement can be present four months after the onset of symptoms and also at least twelve months after the onset. We would suggest that enlargement occurs early and is principally due to the enlargement of the nerve cells which force apart the dense network of astrocytic fibres. With the passage of time the enlarged nerve cells disappear and are replaced by glia but the grey lamina does not shrink.

We also noticed that the more marked enlargement was found associated with the oldest lesions (Case 3), i.e. lesions which were at least one year old. We would suggest that the changes which give rise to the enlargement of the olive proceed over a long period of time, at least in some patients. If the enlargement of the olive is causally related to myoclonus of the soft palate, pharynx, larynx, etc., the suggestion of a long-standing progressive process would receive some support from the fact that in certain patients the myoclonus is seen to involve more and more muscles in the course of the disease.

Summary and Conclusions

Three cases of enlargement of the olive are presented.

(1) The changes in the olive consisted of (*a*) lesions of nerve cells: marked vacuolation, loss of cells and, in one case in which a convenient histological technique was applied, hypertrophy of cell body and cell processes. (*b*) An astroglial and microglial reaction in the grey lamina. (*c*) Pallor of various degree of the amiculum and intra-olivary fibres in sections stained for myelin. Such findings are similar to those reported by previous authors.

(2) Associated lesions in brain-stem or cerebellum consisted of (*a*) In 2 cases, damage to the tegmentum of the pons, especially damage to the central tegmental tract; in one case damage to the dentate nucleus. Such sites of lesions are similar to those reported by previous authors. (*b*) In 2 cases, the lesions were of vascular origin, as in most of the cases previously reported. In the third case the lesion was a syrinx involving the tegmentum of the pons. This case is the one referred to by Dr. Greenfield on page 309 of Greenfield, 1958, but so far as we know such a lesion has not previously been reported in full in association with olivary enlargement. (*c*) In every case the olivary changes were bilateral but showed a very marked predominance on one side. The more affected olive was on the same side as the damaged central tegmental tract or on the side opposite to the damaged dentate nucleus. Such anatomical associations are similar to those previously reported.

(3) The possibility, that damage to a particular group of fibres within the central tegmental tract might account for the olivary changes, has been examined. It is concluded that it appears impossible to ascribe with

certainty such a role to a particular component of the central tegmental tract.

(4) The possibility that retrograde changes could account for the association of olivary enlargement with damage to the dentate nucleus has been investigated. It is concluded that retrograde changes do not provide a satisfactory explanation for the olivary changes.

(5) Changes in the olive associated with damage to the central tegmental tract are likely to be mediated by transsynaptic degeneration. The phenomenon of vacuolation of nerve cells is examined with regard to transsynaptic degeneration.

(6) The enlargement of the olive is found to be due to enlargement of both grey and white matter. The grey lamina is both broader and longer than normal. Evidence is presented to show that (*a*) the enlargement of the contents of the olivary sac is probably passive and secondary to elongation of the grey lamina. (*b*) Enlargement of the grey lamina occurs early in the course of the disease and is partly, at least, due to enlargement of the nerve cell bodies and processes. (*c*) Enlargement of the grey lamina is progressive.

(7) It is suggested that subsequent atrophy of nerve cells is not followed by collapse of the dense glial network.

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LEGENDS FOR PLATES

PLATE XLI

FIG. 1 (*Case* 1).—A, Pons. Loyez myelin stain. ×3. B, Medulla. Loyez myelin stain. ×3. C, Portion of right olive. Hæmatoxylin and van Gieson. ×150. For description *see* text.

PLATE XLII

FIG. 2 (*Case* 2).—A, Right cerebellar hemisphere. B, Medulla. Loyez myelin stain ×3. C, Portion of ventral lamina of left olive. Thionin. ×150. D, Portion of left olive. Modified Bielschowsky for neurofibrils. ×60. E, Olivary nerve cell with an enlarged cell body and enlarged cell processes. Modified Bielschowsky for neurofibrils. ×500. For description *see* text.

PLATE XLIII

FIG. 3 (*Case* 3).—A, Pons. Loyez myelin stain. ×2·5. B, Medulla. Loyez myelin stain. ×5. C, Portion of dorsal lamina of left olive. Thionin. ×150. For description *see* text.

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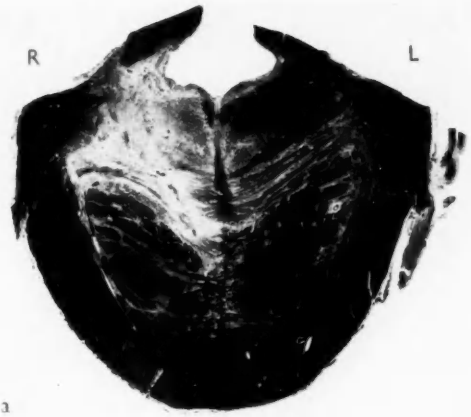
PLATE XLI



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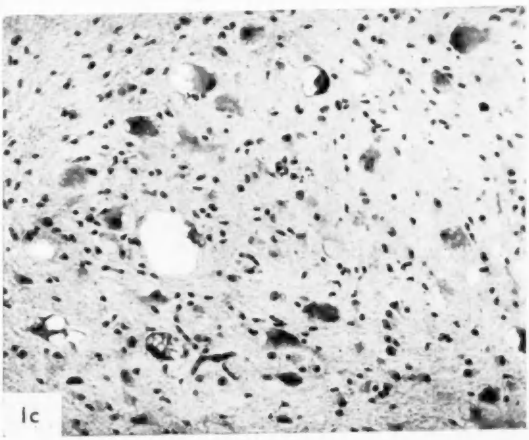

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To illustrate article by J. C. Gautier and W. Blackwood.

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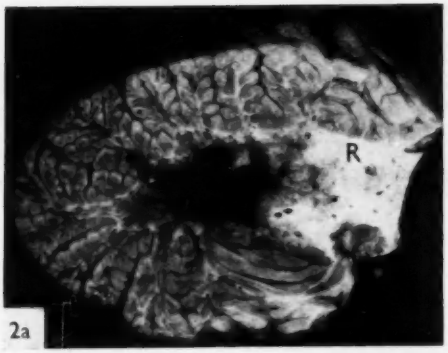
PLATE XLII



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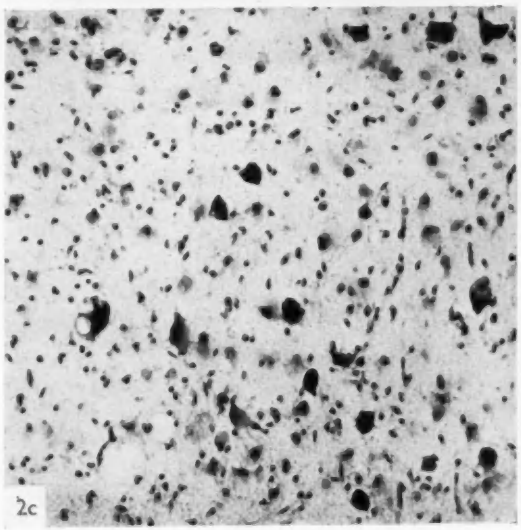
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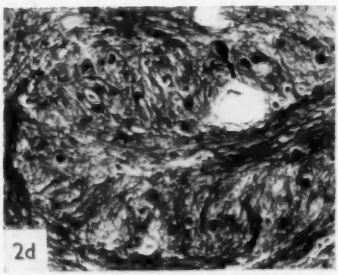
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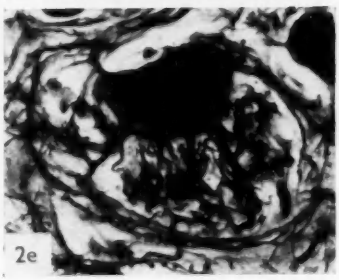
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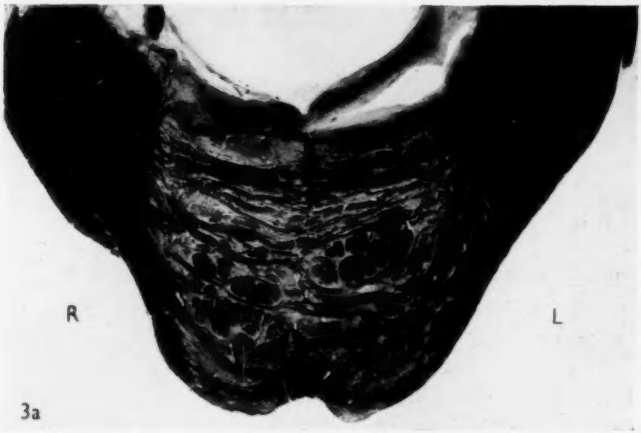
PLATE XLIII



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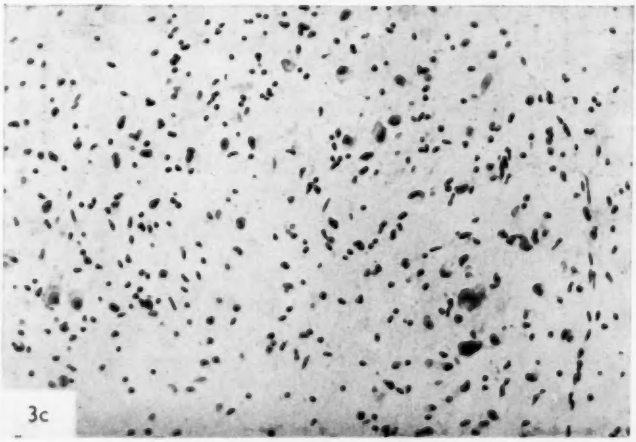

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ARREST OR ACCELERATION OF SPEECH EVOKED BY THALAMIC STIMULATION IN THE COURSE OF STEREOTAXIC PROCEDURES FOR PARKINSONISM

BY

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ELECTRICAL stimulation in the course of stereotaxic operations have aroused considerable interest. Talairach *et al.* (1949), Hécaen *et al.* (1949) have carried it out in the course of thalamic coagulation for intractable pain; Hassler and Riechert (1954) in the course of the surgery of the dyskinesias. We ourselves have studied routinely the effects of deep stimulation before destroying the selected region in the treatment of Parkinsonism. This possesses a double interest: (1) To try to identify each of the three deep sectors traversed by the needle (thalamus, internal capsule, pallidum): (2) to observe the effects of these stimulations upon the different symptoms of the disorder (tremor, rigidity, motility, and speech). The effects of such stimulations are extremely varied, but predominantly motor. We have previously studied the varieties of motor response and the conclusions which can be drawn from them concerning the topographical situation and physiology of the motor pathways in the posterior limb of the internal capsule (Guiot *et al.*, 1959). But we have also observed that stimulation can equally modify speech (and the voice): either by suddenly stopping it, or—and this is a more curious effect—by hastening its delivery. These modifications of speech can occur either in association with other kinds of response, in particular motor, or in isolation. It is the phenomena of arrest, or conversely of acceleration of speech, which we propose to describe here.

Speech has been studied in the following way. The subject is asked either to speak spontaneously, or—and this what seems a simpler method—to count aloud, slowly and regularly, if possible at a rhythm of one number per second. Some attempts are made before the stimulation in order to make sure of the strength of the voice, and that the delivery and enunciation are quite regular. When the patient reaches the figure four or five, the

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stimulation is set going for two to four seconds, either monopolar or bipolar, at a rhythm of fifty to sixty impulses per second, each impulse (rectangular and unidirectional) lasting one millisecond. The voltage is variable according to the case, the point where the stimulus is being applied, and in relation to whether the stimulation is monopolar or bipolar. It is usually effective with half or two-thirds of the voltage which is necessary to obtain a threshold motor response using a single impulse of one millisecond repeated from second to second. (If for example this latter mode of stimulation provokes a motor response with four volts, the voltage for a volley of impulses is initially reduced to two volts.) The needle has a diameter of 2·4 mm.; the two poles (of which one is at the end of the needle) are 1 mm. long and separated by an isolating disc of 1 mm.[1].

In such conditions speech may be (1) unchanged, (2) arrested, or (3) accelerated.

(1) In the first case the patient continues to count regularly with the same rhythm and same force of voice (Diagrams 5 and 6).

(2) *Arrest of speech.*—At other times there is a sudden arrest of the enunciation of the figures: as soon as the stimulation is begun, the patient stops counting; sometimes he has time to enunciate quickly and in a stifled voice the next figure (as shown in Diagram 2). Generally, when the stimulation is terminated the patient begins to count again only if one asks him to. He then starts again at the figure at which he was stopped. Sometimes this arrest is incomplete: in diagram 10 the patient's hesitation is represented by the appearance of slowing.

(3) *Acceleration of speech or tachyphemia.*—On other occasions, finally, there is observed during the first period of stimulation an acceleration of the enunciation of the figures. This is shown in many of the figures, which show a chronometric transcription of speech registered on a magnetic band in the course of the observation. In diagram 1 the patient reaches the figure eight at the end of the stimulation: if he had counted steadily he would only have reached figure six. In diagram 7 the patient stopped at figure twelve half a second before the end of stimulation: if the delivery had remained steady, he would have pronounced the figure nine just at the end of stimulation. In diagram 8 the patient reached eleven instead of seven.

Analysis of the Phenomenon of Acceleration

If we analyse this phenomenon in detail, we note the following characteristics. (1) The phenomenon of acceleration, which we may call tachyphemia, is most often a genuine acceleration, i.e. a progressive augmentation of the speed of enunciation, as one can see in the figures where the

[1]We are grateful to Dr. J. Bates of the National Hospital for having kindly provided us with a model of this needle.

test yielded a positive result. It is rare for the enunciation as in diagram 7 to pass sharply to a more rapid but regular rhythm. (2) This acceleration is usually accompanied by a progressive diminution in the sound of the voice, the last figures enunciated becoming hardly audible or being lost in an inarticulate stammering. We have tried to represent this in the illustrations by giving the figures height proportional to the force of the voice. (3) The phenomenon appears to be conscious, and the patients are subsequently critical of it. If one asks them why they did not continue to count steadily, they invariably reply: "I don't know." And if one persists, one will say: "There was something in me which forced me to hurry"; another: "It is the electric current which does that"; or again: "It is like an impulse to go faster." The majority of patients stop counting at the end of the stimulation, or even before the end: they begin again only if one asks them to. But then the first figure which they utter is the one which follows that at which they stopped. The phenomenon, then, seems to be both conscious and uncontrollable, and patients who try to oppose it fail. (4) Finally, in certain cases, after having accelerated the speech during the stimulation, the patient thereafter continues to count for a longer or shorter time at a rapid rhythm. Once released, the phenomenon therefore can outlast the stimulation. Diagrams 3 and 4, and 7 and 8 are examples of prolonged tachyphemia (7 and 8) or secondary tachyphemia (3 and 4).

Such are the two types of modification of speech which can occur in the course of electrical stimulation by a volley of impulses. These two modifications, apparently mutually opposed, can nevertheless be combined, and that in two forms: either an arrest of speech occurs suddenly during stimulation, and is followed once the stimulation is ended by an acceleration. Arrest, then secondary tachyphemia, is shown in diagrams 3 and 4. Alternatively, there may be a primary acceleration ending in an arrest before the end of the stimulation, and then a longer or shorter secondary tachyphemia. Primary tachyphemia—arrest—secondary tachyphemia is a possible sequence of events of which the last part of diagram 8 is an example.

These modifications of speech can occur either in isolation or at the same time as other effects of the stimulation. The arrest or acceleration of speech can be evoked without any other associated phenomenon—motor, sensory, psychological, or autonomic—either perceived by the patient or noticeable by the observer. At other times the patient says that he felt at the same time an "electric current in the arm or in the hand" on the opposite side to the stimulation, but without anything perceptible in the buccopharyngeal or facial areas. Sometimes there occurs at the same time either a sudden and immediate tetanizing contraction in the hand and face, or even in the half of the body on the opposite side, or a delayed and progressive tonic movement with elevation of the arm, hemifacial spasm, and rotation of the head and eyes to the opposite side.

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Finally, one may observe at the same time an accentuation of the tremor, or its re-establishment if it had previously ceased, as has been observed by Hassler (1957), Hassler, *et al.* (1960).

The Localization of the Stimulus

Before discussing the physiological significance of the phenomena of arrest or acceleration of speech, it is necessary to recall briefly the technique which has been used and to indicate precisely the spot where the stimulus has been applied. In the routine technique (*see* Guiot *et al.*, 1958) the needle enters the parietal lobe. It is directed downwards and forwards, following a strictly parasagittal course (at a distance from the medioventricular plane varying between 15 and 21 mm) and in the direction of the baseline CA-CM (anterior commissure–premammillary groove), which it reaches perpendicularly at a variable height: either at the inferior margin of the anterior commissure, or a little lower at the junction of the superior fifth and inferior four-fifths, superior quarter and inferior three-quarters or superior third and inferior two-thirds of the line CA-CM (fig. 1A).

The diagrams illustrate cases in which the co-ordinate of width was 17 mm. or 18 mm. and the co-ordinate of height ended at the junction of the superior third with the inferior two-thirds of the line CA–CM. (This base-line was itself identified on the outline of the third ventricle rendered visible by lipiodol.)

When the tip of the needle reaches the baseline one knows that it is in the pallidum internum. When the needle is gradually withdrawn, it leaves the pallidum at 6 or 7 mm. on the average behind the baseline, then crosses the posterior limb of the internal capsule (4·5 mm. on the average) and enters the ventrolateral nucleus of the thalamus, which it reaches at 11 or 12 mm. on the average behind the CA–CM line. In each of these three situations the effect of stimulation was observed.

Experience shows that on a plane 17 mm. from the middle line the majority of positive motor responses are achieved between 10 and 24 mm. behind the base-line[1] and that the majority of modifications of speech are obtained at 12 to 14 mm. behind the base-line. The extreme limits range from 8 to 18 mm. on increasing the voltage. If the co-ordinates are placed on the charts of our anatomical atlas, it is clear that the needle is generally in the ventrolateral nucleus of the thalamus when stimulation provokes the arrest or acceleration of speech.

[1]We know now that the muscular responses (sharp localized contractions) which are obtained in the course of this passage through the thalamus (from 24 to 10 mm. behind the base-line) with monopolar stimulation and isolated impulses of 1 millisecond spaced from second to second are the consequence of the lateral spread of the current to motor fibres of the internal capsule. These motor fibres are situated in the posterolateral half of the posterior limb of the internal capsule, with a relative somatotopic localization from behind forwards as follows: lower limb, upper limb, and face, these three territories largely overlapping one another.

Physiological Considerations

Can one say as much as that the modifications of speech (as elsewhere the increase or re-establishment of tremor) are the consequence of the specific stimulation of the ventrolateral nucleus of the thalamus? Several considerations forbid a conclusion as definite as this. (*a*) One must first note that in the parasagittal plane 17 mm. from the middle line the needle is near the external limit of the thalamus. At 14 mm. behind the base-line, and still more 12 mm. (*see* fig. 3), the needle can, owing to the unforeseeable chances of individual variations, be either in the thalamus, or in the thalamocapsular border, or in the internal capsule itself. (*b*) Diffusion of the current, although limited by the bipolar stimulation, is another reason for caution. For the effects obtained could be the consequence not of thalamic stimulation, but of stimulation of neighbouring structures. And the point just made, namely the proximity of the capsule, rendered it impossible to exclude for certain the possibility of activation of the internal capsule which might have been responsible either for the tremor or the dynamic modifications of speech. For example, diagram 3 shows a secondary tachyphemia obtained when the electrode was, it was deduced, in the internal capsule. (*c*) Finally, stimulation by a volley of impulses can excite a number of positive responses which vary according to individual patients and of which the origin may be quite remote from the point stimulated.

The physiological explanation of the phenomena are no less difficult to offer. It was tempting to consider that the acceleration of speech evoked by electrical stimulation in Parkinsonian patients was the experimental reproduction of the symptom called after Claude "paroxysmal tachyphemia." In Parkinsonism, that is to say, speech may be suddenly accelerated and become precipitate as well as produced by a weak and toneless voice (Monrad-Krohn's dysprosody, Marie and Lewy's aphonic tachyphemia). The phrase may end with the repetition of the last word (stereotyped tachyphemia or palilalia of Souques) or lose itself in a persistent murmur. This, it appears, is what is produced in certain cases—acceleration of speech, progressive weakening of the voice, and an enunciation which ends in a kind of incomprehensible jumbling of several figures or the palilalic repetition of the last figure uttered. This assimilation seemed also to be confirmed by the possibility of evoking from the same spot a recurrence or an augmentation of the Parkinsonian tremor.

However, we know from Talairach[1] that the same phenomenon has been observed in a patient who was not Parkinsonian, following a stimulation performed in an area of the brain very distant from that where ours was sited. If both observations are accepted, one must abandon this hypothesis or admit that the acceleration of speech is simply facilitated in

[1]Personal communication.

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Parkinsonians by the fact of their tendency to exhibit verbal modifications of this type.

Are we dealing with a purely motor phenomenon? This idea is applicable to the arrest of speech when it accompanies a tetanizing contraction with respiratory spasm during the period of stimulation. But, as we have seen, the motor responses are not necessarily associated with verbal modifications. And what sort of motor stimulation could explain the acceleration of speech? Recently Hassler *et al.* (1960) said that they have observed, while stimulating the pallidum (with frequencies of 25/second and thereabouts) an inhibition of voluntary movement and speech; and, whilst stimulating the oral-ventral nucleus of the thalamus, a state "of general excitation accompanied by indistinct verbal expressions and sudden elevation of the opposite arm." This effect, according to these authors, resembles those produced by stimulation of the supplementary motor area of Penfield and Welch (1951).[1] It is possible that the acceleration of speech which we have observed is a physiological phenomenon of the same order—a phenomenon of psychomotor stimulation, as the comments of our patients suggest: "There is something in me which forces me to hurry"... "It is like an instinct to go faster"...

[1](Penfield and Welch have observed, as the result of stimulation of the lower Rolandic area and the supplementary sensorimotor area, either an arrest, a hesitation, or a slowing of speech, or, conversely, a vocalization (more voluntarily rhythmical when excited from the supplementary area). But the precise phenomenon of acceleration of speech has not been described.

In spite of the difficulty of the interpretation, the phenomena of arrest and acceleration of the speech under the influence of deep cerebral stimulation are in themselves sufficiently curious to justify the description which we have tried to give.

SUMMARY

This is a study of the modifications of speech evoked by electrical stimulation in the course of operations for Parkinsonism. These modifications are of two types: sometimes arrest of speech, which is the commoner phenomenon; sometimes acceleration of the delivery of speech, a rarer but very special phenomenon, the physiological significance of which is discussed. The point stimulated was situated in the ventrolateral nucleus of the thalamus near the thalamocapsular boundary.

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(See over for figures)

CAPTIONS TO FIGURES AND DIAGRAMS

FIG. 1A.—Schematic representation of direction of the needle (1) sagittal (2) perpendicular to the base-line CA–CM.

FIG. 1B.—Histological sections following the path of the needle. The left hand figure is a horizontal section perpendicular to the base line CA–CM and passing through the junction of the superior one-third with the inferior two-thirds of that line. The line CA–CM is shown by two horizontal markers. There are 2 mm. between each intersection of the squares. The figure on the right is a sagittal section passing 17 mm. from the middle line. CA–CM is shown by two vertical markers. The perpendicular to the base-line CA–CM passing through the lower border of CA is shown by two horizontal markers. The three essential landmarks of the third ventricle are shown as follows: CA (ovale); CM (angle opening upwards showing the pre-mammillary groove); CP projection into the postero-inferior part of the thalamus. There is 1 mm. between each intersection of the squares.

FIG. 2.—Operation arrangements. 1 and 2, Guides and sites. 3, Electrode. 4, Target point. 5, Ventricular projection of target point. 6, Medioventricular plane. 7, X-ray screen and amplifier. 8, X-ray tube. The X-ray screen (7) and the X-ray tube (8) are in one piece. The distance between the two is 1·10 m. The head of the patient, the guides, and the X-ray apparatus, are respectively moved until the exact superimposition of the two sights and the ventricular projection of the target point (1, 5 and 2) is achieved. The needle (3) is then advanced to the target point (4) according to the co-ordinate of width which has been chosen.

FIG. 3.—Tracings of 20 horizontal cuts, perpendicular to base-line CA–CM, at a height corresponding to the junction of the superior one-third and inferior two-thirds of the base-line (using an anatomical atlas made in collaboration with S. Brion, W. Reichenbach and M. Ackerman). The sagittal line corresponds to the medio-ventricular plane. Horizontal line passes through the base-line CA–CM. The red point indicates the position of the needle at 14 mm. behind CA–CM. This figure shows the variations in the position of the electrode in relation to the thalamocapsular boundary: 15 times out of 20 the red point is frankly in the thalamus, 3 times out of 20 it is at the thalamocapsular boundary, and twice out of 20 times it is in the internal capsule. If the red point were situated at 12 mm. behind the base-line, its situation would be still more indefinite.

FIG. 4.—Diagram 1.—A, aged 47 years, bilateral Parkinsonism, predominating on the left side. Operation on the right hemisphere (non-dominant). The needle was advanced to 17 mm. from the medioventricular plane in the direction (perpendicular) of the base-line CA–CM, which it met at the junction of its superior third with its inferior two-thirds. The effect of tachyphemia was obtained at 14 mm. behind the base-line CA–CM. Above the chronometric transcription of speech two sections have been traced. The left section is a horizontal section at the same height; it corresponds to the statistically average case. The right section is a parasagittal section at 17 mm. from the middle line (statistically average case). On this section, the profile of the third ventricle is in red. On each of the two sections the red point shows the spot at which tachyphemia was elicited.

Diagrams 2–5.—G, aged 51 years. Bilateral Parkinsonism, more severe on the right. Operation in the left hemisphere (dominant). The co-ordinates of the needle are: breadth (z) = 17 mm., height (y) = one-third superior to two-thirds

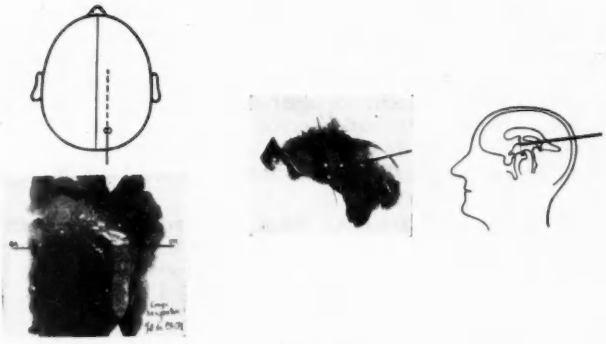


FIG. 1A.

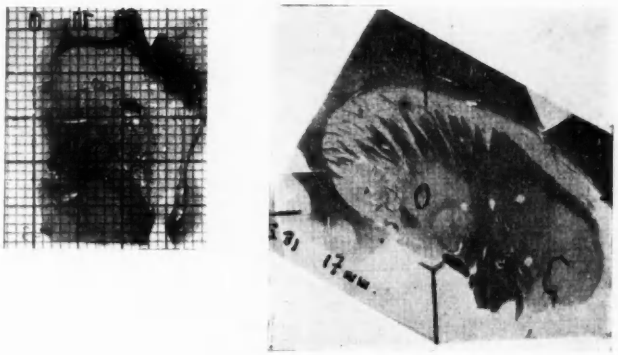


FIG. 1B.

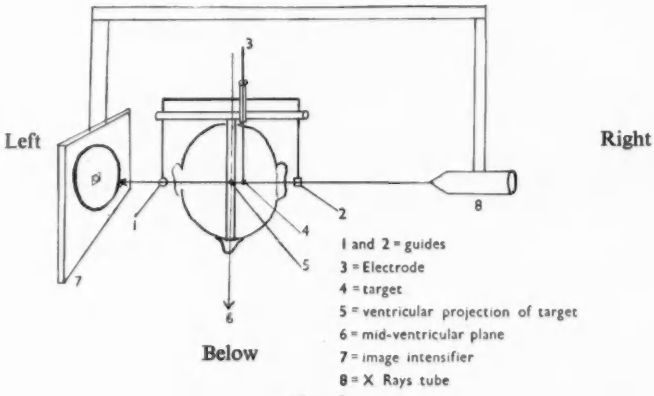


FIG. 2.

inferior of CA–CM. Length (x) = red points. Four successive tests were made: at 8 mm. behind CA–CM (Diagram 2), 10 mm. behind CA–CM (Diagram 3), 12 mm. behind CA–CM (Diagram 4), 14 mm. behind CA–CM (Diagram 5). For each test the situation of the needle is shown by a red point on the horizontal and parasagittal sections (chosen for their statistically most frequent situation). If the anatomical structure of the patient corresponds to these sections, one sees that the same phenomena (secondary tachyphemia and provoked tremor) were obtained as well when the needle was in the internal capsule as when it was in the thalamus.

Diagrams 6–10.—C, aged 53 years. Right hemi-Parkinsonism. Intervention in the left hemisphere (dominant). The co-ordinates of the needle are: breadth (z) = 18 mm., height (y): one-third superior to two-thirds inferior of CA–CM. Length (x): red points. Tachyphemia at 12, 14 and 16 mm. behind CA–CM.

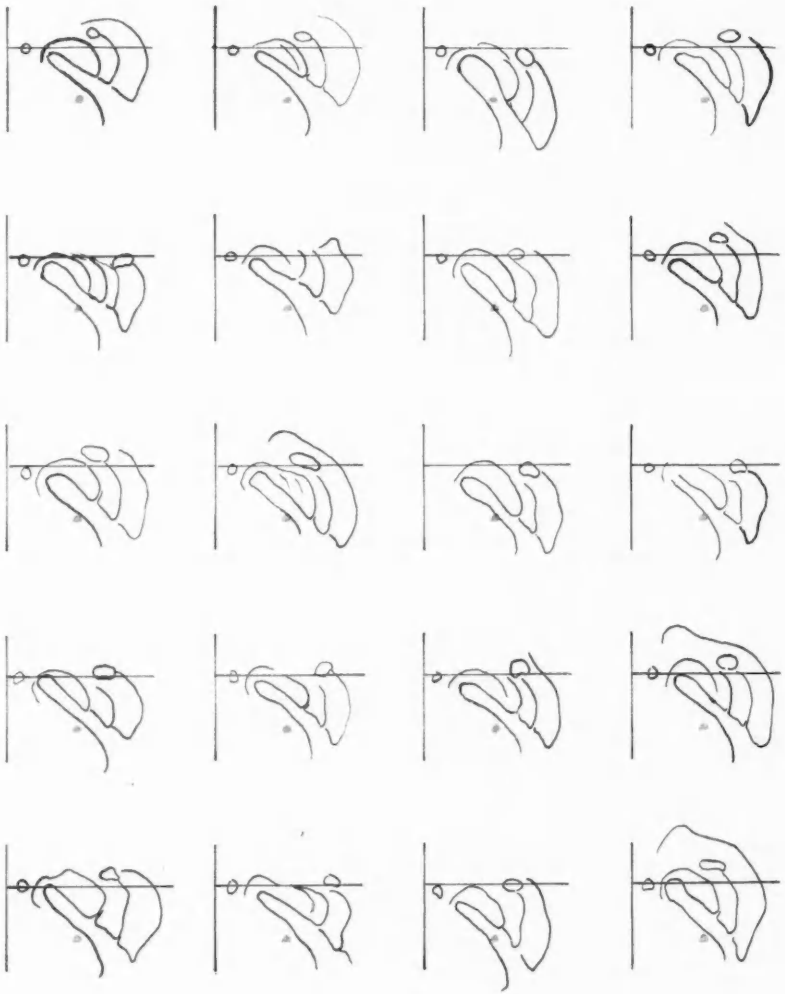
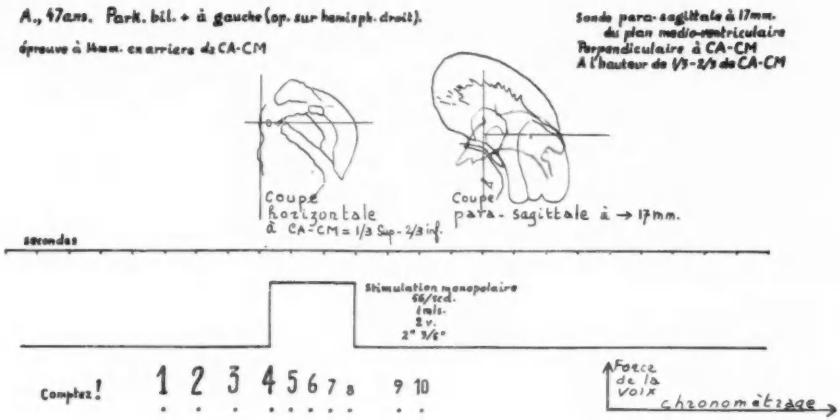


FIG. 3.


A., 47ans. Park. bil. + à gauche (op. sur hemisph. droit).
épreuve à 14mm. en arrière de CA-CM
Sonde para-sagittale à 17mm. du plan medio-ventriculaire
Perpendiculaire à CA-CM
A l'hauteur de 1/3-2/3 de CA-CM
Coupe horizontale à CA-CM = 1/3 Sup-2/3 inf.
Coupe para-sagittale à → 17mm.
secondes
Stimulation monopolaire
66/sec.
1 mls.
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2" 3/5"
Comptez! 1 2 3 4 5 6 7 8 9 10
Force de la voix
chronomètrage

FIG. 4.—DIAGRAM 1.

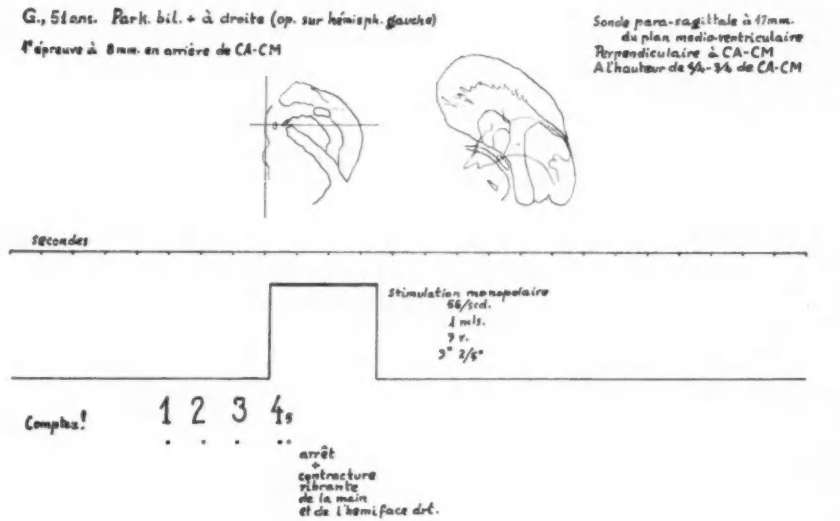
G., 51ans. Park. bil. + à droite (op. sur hémisph. gauche)
1ère épreuve à 8mm. en arrière de CA-CM
Sonde para-sagittale à 17mm. du plan medio-ventriculaire
Perpendiculaire à CA-CM
A l'hauteur de 1/4-3/4 de CA-CM
secondes
Stimulation monopolaire
66/sec.
1 mls.
2 v.
3" 2/5"
Comptez! 1 2 3 4
arrêt + contracture vibrante de la main et de l'hemiface dct.

FIG. 4.—DIAGRAM 2.

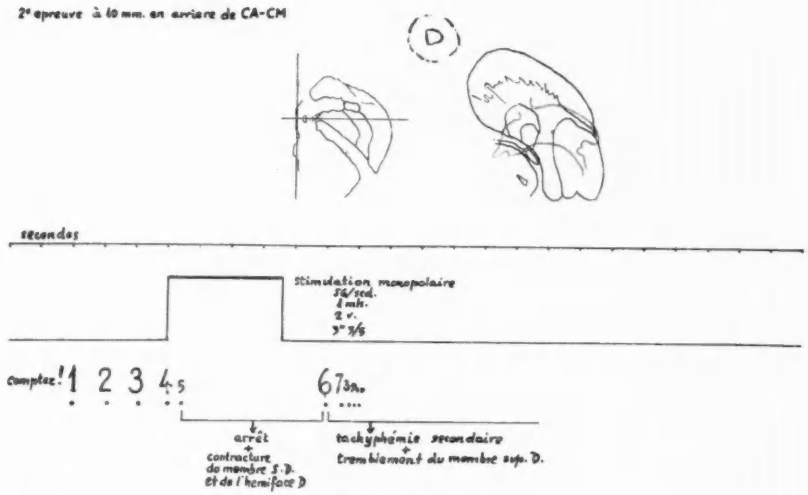

FIG. 4.—DIAGRAM 3.

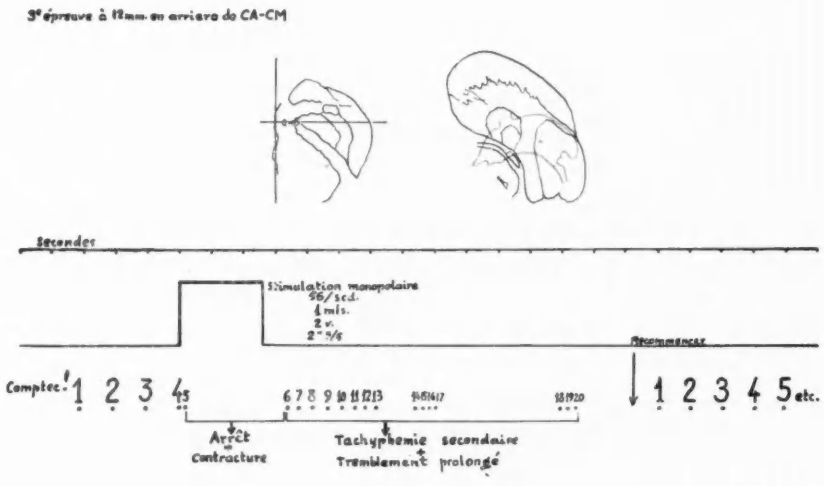
3e épreuve à 12mm. en arriere de CA-CM
Secondes
Stimulation monopolaire
56/scd.
1 mls.
2 v.
2" 5/6
Recommencez
Comptez: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 1 2 3 4 5 etc.
Arrêt
Contracture
Tachyphémie secondaire
Tremblement prolongé

FIG. 4.—DIAGRAM 4.

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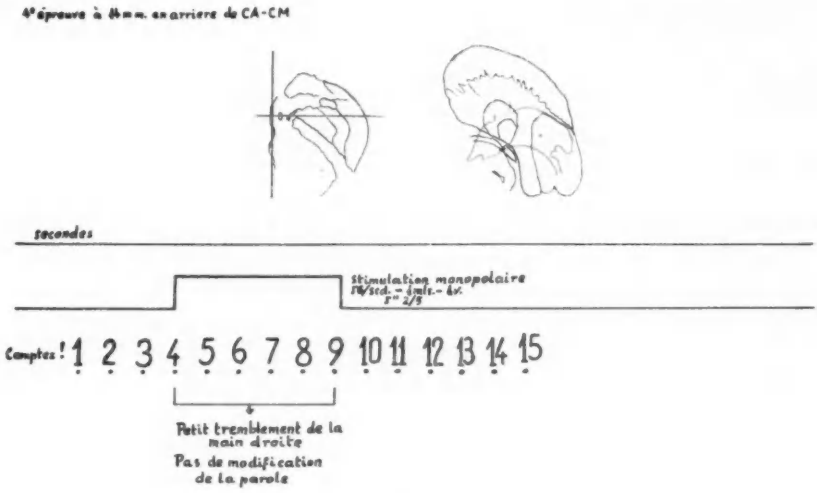
4e épreuve à 16 m.m. en arrière de CA-CM
secondes
Stimulation monopolaire
Comptez ! 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Petit tremblement de la main droite
Pas de modification de la parole

FIG. 4.—DIAGRAM 5.

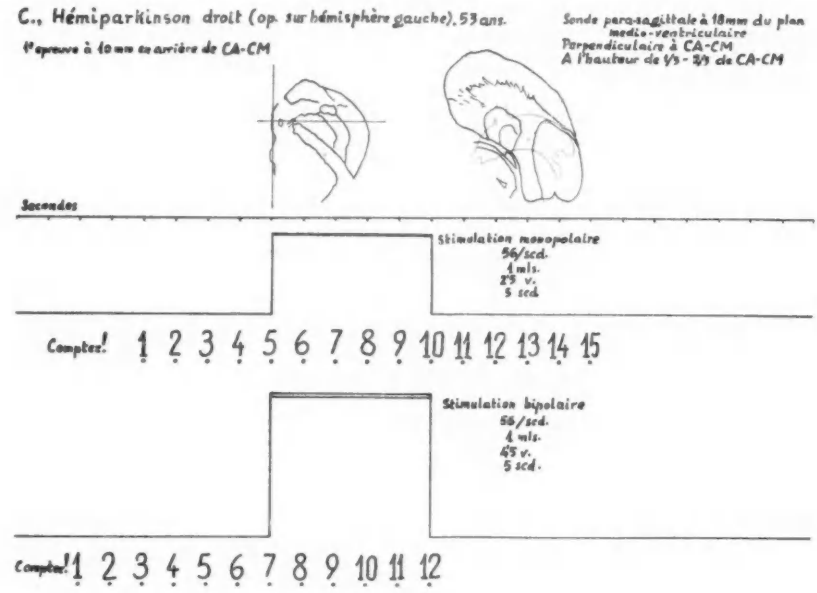
C., Hémiparkinson droit (op. sur hémisphère gauche). 53 ans.
4e épreuve à 10 mm en arrière de CA-CM
Sonde para-sagittale à 18mm du plan médio-ventriculaire
Perpendiculaire à CA-CM
A l'hauteur de 1/3 - 2/3 de CA-CM
Secondes
Stimulation monopolaire
56/scd.
1 mls.
2,9 v.
5 scd.
Comptez ! 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Stimulation bipolaire
56/scd.
1 mls.
4,5 v.
5 scd.
Comptez ! 1 2 3 4 5 6 7 8 9 10 11 12

FIG. 4.—DIAGRAM 6.

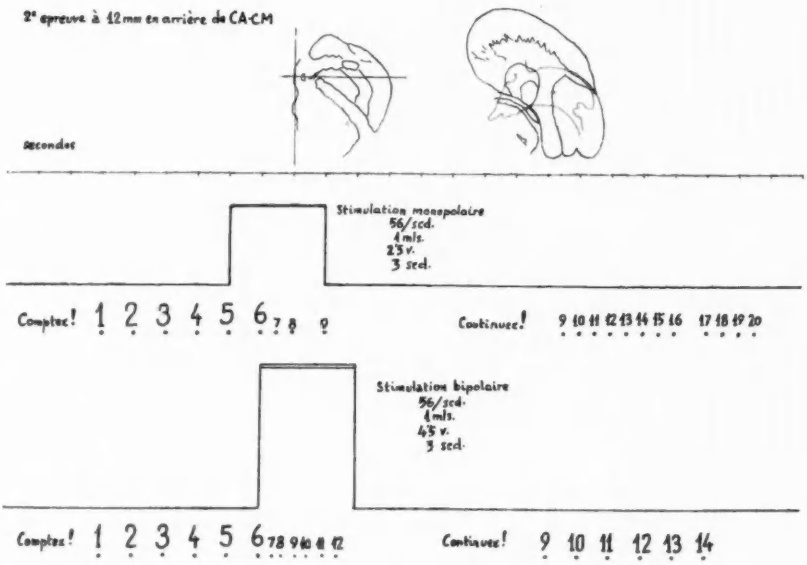
2e épreuve à 12mm en arrière de CA-CM
Secondes
Stimulation monopolaire
56/scd.
4 m/s.
23 v.
3 scd.
Comptez! 1 2 3 4 5 6 7 8 9
Continuez! 9 10 11 12 13 14 15 16 17 18 19 20
Stimulation bipolaire
56/scd.
4 m/s.
43 v.
3 scd.
Comptez! 1 2 3 4 5 6 7 8 9 10 11 12
Continuez! 9 10 11 12 13 14

FIG. 4.—DIAGRAM 7.

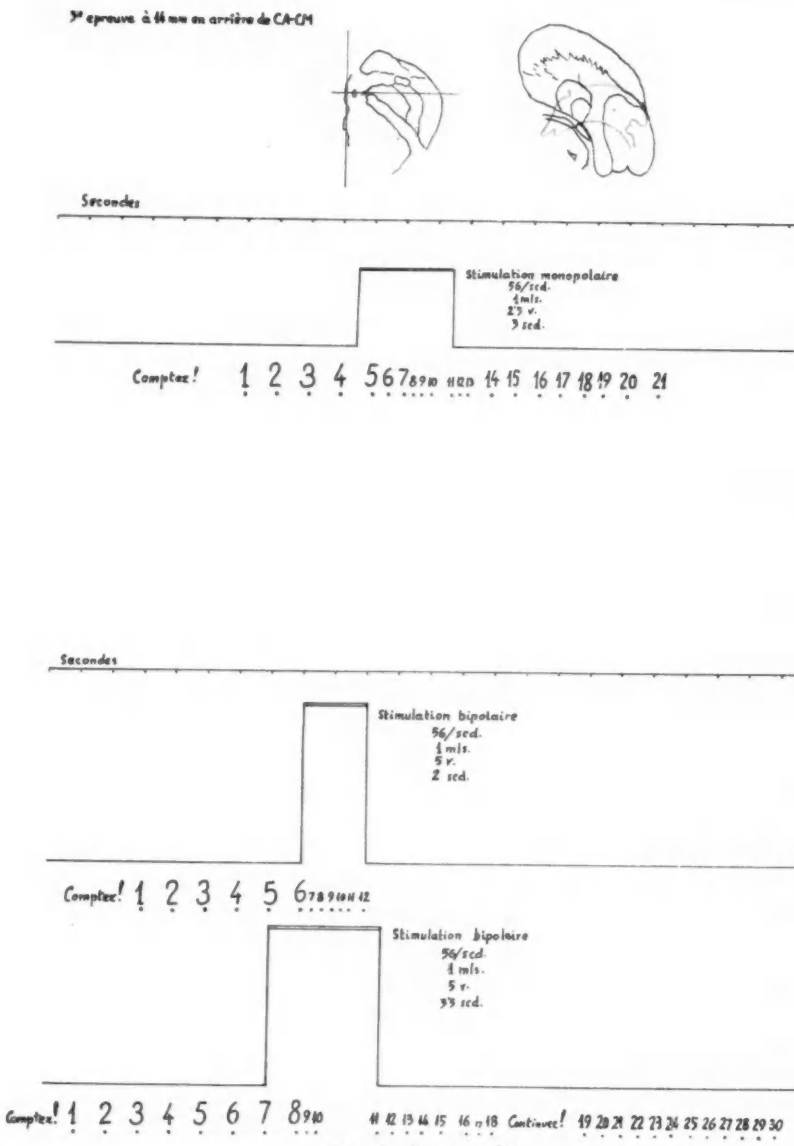
3e epreuve à 46 mm en arrière de CA-CM
Secondes
Stimulation monopolaire
56/sec.
1 mls.
23 v.
3 sec.
Comptez! 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Secondes
Stimulation bipolaire
56/sec.
1 mls.
5 v.
2 sec.
Comptez! 1 2 3 4 5 6 7 8 9 10 11 12
Stimulation bipolaire
56/sec.
1 mls.
5 v.
33 sec.
Comptez! 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 Continuez! 19 20 21 22 23 24 25 26 27 28 29 30

FIG. 4.—DIAGRAM 8.

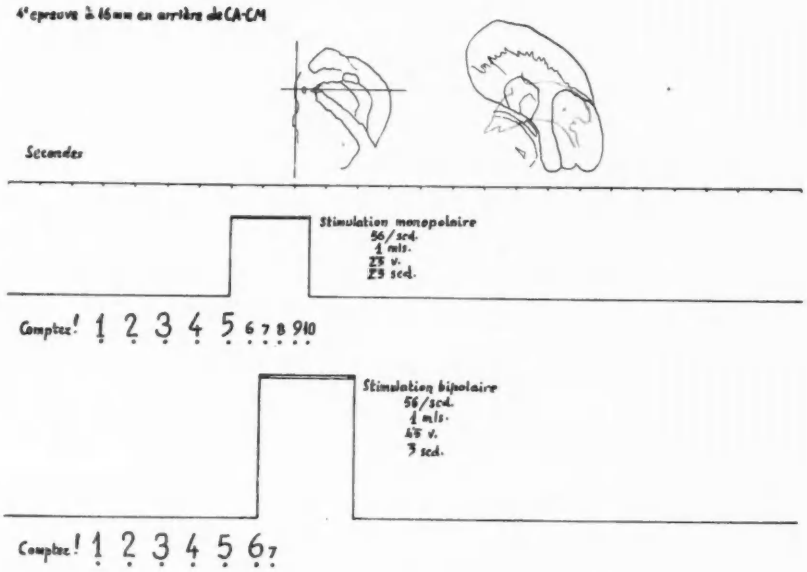

FIG. 4.—DIAGRAM 9.

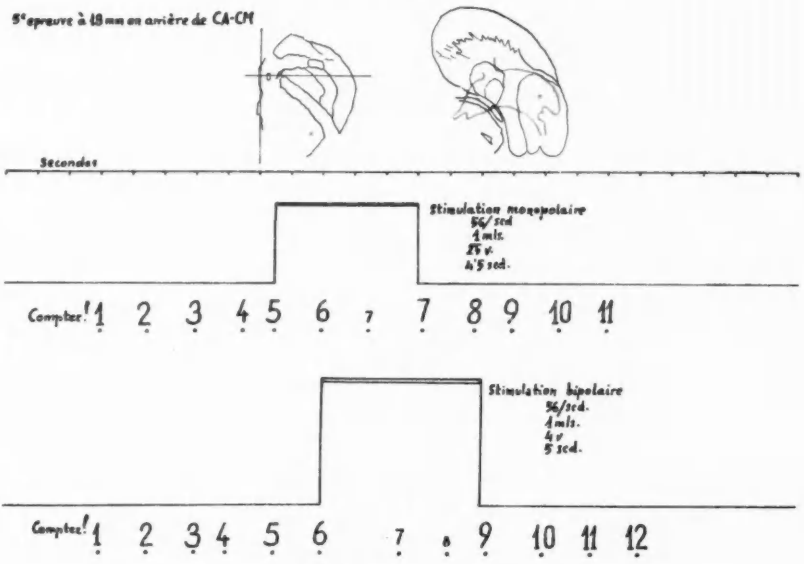

FIG. 4.—DIAGRAM 10.

POST-EPILEPTIC PARALYSIS: THEORETICAL CRITIQUE AND REPORT OF A CASE

BY

ROBERT EFRON[1]

> "The only thing that makes me sigh is when men, especially old pupils, write on a subject I have gone into in the Manual and never refer to what I have said."
>
> SIR WILLIAM GOWERS (1903).

THE transient paralysis of an arm or a leg following a seizure has been reported in great detail since the first description by Bravais in 1827. It would be unnecessary to report one more such example were it not for the fact that this particular case illustrates the major weakness in the prevailing theory which ascribes the post-epileptic paralysis to "exhaustion" or "anoxia" of the nerve cells involved in the preceding seizure.

Historical Development of Todd-Robertson Hypothesis

Bravais (1827) in his description of the unilateral seizures (subsequently called "Jacksonian seizures" by Charcot) also called attention to the paralysis which followed the attack (subsequently called Todd's paralysis). He used the term "hemiplegie epileptique." In "Clinical Lectures" Todd (1855) making no reference to Bravais, described the paralysis as "epileptic hemiplegia" and added the idea that the paralysis is due to exhaustion of the neurons. Alexander Robertson (1869) supported Todd's explanation that the paralysis is due to exhaustion.

Hughlings Jackson had come to the same conclusion independently, but in his later writings (1876) he attributed authorship of this hypothesis to both Todd and Robertson. He thereafter always referred to it as the "Todd and Robertson's Hypothesis." Scarcely a paper of Jackson's fails to mention epileptic hemiplegia (which he renamed "post-epileptic paralysis") and his support of the Todd-Robertson hypothesis. Todd's theory of its causation assumed great significance in his subsequent thinking about such other postictal phenomena as confusion, mania, aphasia, stupor and coma.

Sir William Gowers (1881) objected to the Todd-Robertson hypothesis as the explanation for all cases.

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> "It is not easy to explain on this theory all the phenomena of post-epileptic paralysis. It is difficult to explain as an effect of 'exhaustion' the extreme weakness which may exist in the arm, and occasionally in the leg, after a slight local fit. The difficulty is increased if we regard the exhaustion as affecting chiefly the nerve fibres, which are not readily exhaustible to the extent of causing such loss of power as is sometimes observed. There is also a disproportion between the severity of the fit and the subsequent paralysis. A patient may have a severe general convulsion, and, a few minutes later, may have no conspicuous weakness, while another patient, who has had a fit confined to one arm, apparently slight in degree, may be unable to move the limb for an hour or more. Dr. Jackson has suggested, as an explanation of this discrepancy, that the sudden violent discharge is diffused widely, overcoming widely the resistance, by its force; while the slower local discharge, having more 'momentum,' does not diffuse itself, is concentrated on certain parts, which are thus stimulated for a longer time and in greater absolute degree, and so become exhausted. But there is no evidence that a slight discharge of long duration exhausts the nerve elements more than a severe but brief discharge. Moreover, a comparison of a series of cases shows that there is no relation between either the duration or degree of convulsion, or both, and the subsequent weakness; that on the one hand we may have severe or long-continued motor spasm with very little subsequent weakness; while, on the other hand, great loss of power may succeed other attacks in which there is no motor convulsion, in which the fit consists of a purely sensory discharge."

Jackson as late as 1890 still rejected Gowers clinical observations and insisted that "the post-epileptiform paralysis is—that is, in my experience—always of the parts which were first and most convulsed in the prior fit."

But Jackson himself had reported a case, as early as 1868, in which a patient with focal seizures of the leg had no post-epileptic paralysis until he developed a technique of arresting the seizures by rubbing the calf. Following arrested seizures marked postictal paresis *always* resulted. Gowers also referred to this case in 1881:

> "Another interesting fact, to which Hughlings Jackson has called attention, also affords strong evidence that inhibition, rather than exhaustion, is the chief element in the paralysis after local seizures. It is that the paralysis may be greater if a commencing fit is arrested by the ligature, than if it runs its usual course. The ligature must be regarded as acting on the sensory centre and increasing the resistance in, i.e., inhibiting, the related motor centre. That the subsequent paralysis should be thus increased affords strong confirmation of the view that it depends chiefly upon inhibition, while it is incompatible with the theory that it depends solely on exhaustion."

Dutil (1883) reported a case of a man who had a Jacksonian fit starting in the right foot. On one occasion, after arresting a fit by ligature, he developed a fifty minute paralysis of the right arm which had not been invaded by the seizure. As the paralysis of the arm subsided, he developed progressive aphasia. The aphasia disappeared within twelve hours.

Jackson (1870) attempted to explain the phenomenon of the arrest of seizures by the ligature. He did not, however, refer to the fact that the postictal paralysis is frequently *worse* following arrested (partial) seizures than after completed, more severe seizures.

Jackson's reasoning rested on the assertion that the paralysis was more severe in the regions most convulsed during the fit. It was this clinical assertion that Gowers questioned, for, it if were not true, Jackson could not support the Todd-Robertson hypothesis—a hypothesis which was deeply incorporated in his views on the evolution and dissolution of the nervous system.

Clark (1899) reviewed over 60 published cases of paralysis following seizures (including Dutil's and Jackson's) and reported 40 of his own. He was strongly in favour of the exhaustion hypothesis but stated that "The duration of the paralysis varies extremely and does not appear to bear any special relation to the severity of the convulsion (p. 365)." Yet, in the same monograph he often repeats Jackson's dictum, "Paralysis always follows the general rule, namely, parts most convulsed suffer most in the post-convulsive paralysis (p. 404)." Clark, quite aware of Gowers' views, believed that Gowers was referring mainly to cases of "inhibitory epilepsy" —in cases of paralysis with *no* preceding convulsive movements.

Jackson (1880) at first attempted to differentiate clearly between post-epileptic paralysis and epileptic paralysis (inhibitory epilepsy). Clark (1899) suggested that Gowers confused these two conditions. The fact remains that Gowers was not at all confused. He merely asserted that the two conditions could not legitimately be separated—that they frequently occurred simultaneously. He described several cases of focal *sensory* seizures in which the regions in which the sensory aura was located were simultaneously paralysed. He said,

> "In these cases, then, we have transient paralysis without any motor spasm, i.e., we have lowered activity of the motor centres, but without any discharge in them. We must regard the centres as restrained or inhibited, and it is readily conceivable that a discharge in the related sensory centre should, under certain circumstances, cause such inhibition, just as a painful cutaneous impression will often inhibit or arrest reflex action, a fact well known to physiologists. If such paralysis accompanying a sensory aura is to be thus, and thus only explained, it becomes most probable that the weakness which succeeds a slight attack of local spasm is, in part at least, of the same character . . . "
>
> "The phenomena of some attacks show that, although the conditions of discharge and inhibition are antagonistic and, in high degrees, incompatible and mutually exclusive, yet in partial degrees they may coexist. A centre may be in a state of partial inhibition and partial discharge, and either condition may preponderate and ultimately obtain exclusively . . . "

He also referred to a patient who "always saw colours, especially green and blue, in slight attacks while severe fits were preceded by simple loss of sight."

Nine years later, Jackson (1890) answered Gowers by attributing *both* postictal paralysis and ictal paralysis (inhibitory epilepsy) to the same mechanism of exhaustion.

> "There may be discharge spreading slowly in a motor centre of the middle level, excessive enough to cause slight after-exhaustion of some of its elements, although

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> not one strong enough to overcome the resistance of lowest motor centres, and thereby to produce actual convulsion."

Yet in the same paragraph he continued his previous attempt to differentiate between paroxysmal and post-paroxysmal paralyses. This problem of the classification of the paralytic phenomena associated with seizures will be discussed later in this paper.

In the sixty years that have followed Clark's monograph, Gowers' objections to the Todd-Robertson hypothesis have been largely ignored. The emphasis of modern investigators has centred about attempts to define, albeit more precisely, the physiology of postictal "exhaustion." Stone (1938) using mice showed that the cerebral lactic acid content increased during fits induced with Metrazol, picrotoxin and cyanide. There was no change with nicotine, and an actual *decrease* during fits induced with insulin (hypoglycæmia). Subsequently, Stone, Webster, and Gurdjian (1945) demonstrated an increase of lactic acid content in artificially respired dogs during seizures induced by Metrazol. They correlated the increase of cerebral lactic acid with the fall in pH values measured by Jasper and Erickson (1941). As these changes in lactic acid, as well as phosphocreatine were also present in animals made hypoxic, they attributed the chemical changes to the relative cerebral hypoxia which occurs during seizures. They did not, so far as one can tell, pursue the problem of the fall of lactic acid during hypoglycæmic convulsions. Inasmuch as hypoglycæmic convulsions *also* stop, it would be improper at this point to say that the cerebral acidosis, in itself, is the basis of the postictal state of exhaustion.

In recent years it has become popular to equate the idea of local exhaustion of nerve cells with that of local "anoxia." Penfield (1937, 1939) after his studies of cerebral blood flow during seizures said, "Even though increased circulation does occur there is no reason to conclude that the enormously increased need for oxygen on the part of the neurones is completely satisfied."

Davies and Remond (1947) using the polarographic techniques developed by Davies and Brink (1942) studied the oxygen tension of cerebral tissue during a seizure. They found that a polarographic electrode placed near a cortical vein or capillary showed a reduction of oxygen tension during the course of seizures. This was also found by Davis, McCulloch and Roseman (1944). Davies and Remond explained this reduction quite reasonably, by assuming that the excessively active neurones had an increased oxygen consumption. As these workers used anæsthetized, curarized animals, nothing could be said of the relation of postictal paresis to their oxygen measurements.

More recently still, Meyer and Portnoy (1959) using animals with one occluded middle cerebral artery stated that,

> "Concurrent records of cortical EEG, blood flow, pH and oxygen tension show that postictal paralysis appears to be due to cortical anoxia resulting from the metabolic demand for oxygen outstripping its supply."

They further conclude from their studies that,

> "Rhythmicity of prolonged intermittent seizures characterized in the EEG by bursts of rapid spike activity alternating with quiescence appears to be mediated by corresponding rises and falls in cortical oxygen tension. The seizure exhausts available oxygen supply and there is neuronal quiescence until the oxygen supply is replenished."

As Meyer and Portnoy are the first to have claimed to have demonstrated this thesis experimentally, it is necessary to analyse their data carefully. In the first place, no measurements of EEG, blood flow, cortical oxygen tension, pH, etc., were made on the 5 monkeys who were said to develop the postictal paralysis. Their conclusions were based on observations of the size and colour of pial blood vessels during the ictal and postictal states. A further analysis of cortical refractory states to electrical stimuli was made which again showed merely what Franck and Pitres (1883) demonstrated—that after a seizure the cortical threshold is elevated. Meyer and Portnoy, apparently unaware of Franck and Pitres' experiment, have not only repeated their work, but have fallen into the same logical error. All four workers assume that the increased threshold following a fit necessarily implies that a state of exhaustion (or anoxia) is the cause of the threshold change. A large number of different chemical or electrical events (*see* Eccles, 1957) may alter the threshold of a neurone. One cannot say, therefore, that an increased refractory period *per se*, is a sign of "exhaustion" or "anoxia." Furthermore, Meyer and Portnoy's animals were stated to develop "transient hemiplegic attacks by *any* stimulus which tends to upset the precarious balance between circulatory supply and local metabolic demand." It is hardly surprising then, that electrically evoked seizures in such unanæsthetized, uncurarized animals resulted in a transient hemiplegia when by the authors' own admission other stimuli could also produce the hemiplegia without producing a preceding seizure.

Secondly, in the 11 cats in which measurements of cortical EEG, blood flow, pH and oxygen tension *were* made, curare was used. In this group of animals, therefore, in which the quantitative data were purported to relate to postictal paralysis—the paralysis could not be studied because of the administration of the neuromuscular blocking agent.

Thirdly, they state (in reference to their figures 10 and 11) that "during strychnine seizure activity, the cortical oxygen tension fell to near zero levels (as determined by dead brain at the end of the experiment) at this point cortical spike activity ceased and the EEG record became quiescent." Examination of fig. 10A reveals that the oxygen tension measured with polarographic electrodes *did not change at all* on the side in which the

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vascular supply was normal yet the seizures *still stopped on that side at the same time as they stopped in the hemisphere with reduced vascular supply and diminished oxygen tension.* In fig. 10B, there was a slow decrease of oxygen tension on the normal side, yet the fits on that side followed the same time course as on the operated side which had reduced circulation.

In their fig. 11A, the oxygen tension actually *increased* during seizure activity on the side with a normal vascular tree, *yet the seizure did not last any longer on that side than it did on the side showing decreased oxygen tension.*

It might be proposed, as an explanation for these findings, that the strychnine was applied to the ischæmic hemisphere. This then caused a fit on that side which spread to the normal side. When the oxygen had been depleted on the ischæmic side, the "driving" of the abnormal activity ceased on the normal side. However, examination of the records published by Meyer and Portnoy refutes this possibility as they reveal identical times of onset (to the limits of measurement[1]) in fig. 10A and fig. 10B. In fig. 11A, the fit appeared to start *earlier* on the normal side. Yet, all seizures appeared to stop at the same time. Furthermore, in fig. 9, intravenous Metrazol was used to start the seizure and in this case it was recorded first on the normal side. The change in oxygen tension on the normal side appeared insignificant, yet the seizure lasted as long on this side as it did on the side with reduced circulation.

It may still be argued, as the seizures were of the same duration and time course on the two sides, that the focus of activity was in the mid-line grey matter and that cortex was merely responding to this driving focus. The seizure might thus end because of "exhaustion" or "anoxia" of this central nuclear mass. This would not necessarily be detected in Meyer's experiment as his polarographic electrodes were located on the cortex. There is, however, no data supplied by their experiment to support such an explanation.

It is clear that Meyer and Portnoy have, in fact, shown the very opposite of what they thought they had proven. Using this elegant way of reducing the vascular supply of one region of the brain, and keeping this area as a control, they have inadvertently but conclusively demonstrated that the *duration of seizure activity is unrelated to the changes of oxygen* tension of the surface of the brain. They have actually demonstrated the *absence* of a causal relationship between cortical oxygen tension and duration of seizures.

Davies and Remond published records showing a significant decrease of cortical oxygen tension during seizures, even with the most careful attempts to *avoid* reducing cortical blood flow. They pointed out, however, that

[1]There are no technical means now available to determine the precise moment a seizure starts, as the electrical manifestations of the onset of seizure activity are not unique.

the results of this polarographic method are critically dependent on the location of the polarizable electrode with reference to pial arterioles and veins—the region near arterioles showing no change during a seizure, but the tissue near veins showing a decrease of oxygen tension. Meyer and Portnoy do not give any information about the size and location (vis à vis blood vessels) of their electrodes. In a previous work, Meyer and Denny-Brown (1955) used large electrodes which recorded an "average" oxygen tension of a large area of cortex. If similar electrodes were again used, it might explain why so little alteration was found on the normal side. Yet even this knowledge would not alter the conclusion which must be drawn from Meyer and Portnoy's experiment—namely, that the duration of the seizure in the cortex is unrelated to the reduction of cortical oxygen tension recorded by this sensitive technique.[1]

It is important to stress that Meyer and Portnoy studied two different questions—firstly, the cause of postictal paralysis and secondly, the cause of the termination of seizures. Answers to these two questions are not necessarily related, and the two problems should, until more knowledge is available, be treated separately.

Should Meyer and Portnoy's clinical conclusion that postictal paralysis is more apt to occur when cerebral vascular disease is present be accepted, we are still forced to explain its occurrence in those cases (such as the one they reported) in which there is no demonstrable abnormality. Finally, should it be true that vascular abnormalities do in some as yet unknown way predispose to postictal paralysis, this information would not assist in explaining the phenomena of the following case.

Case Report

This 28-year-old white labourer was in good health until the age of 19 years when a heavy object fell from a truck, hit his head, and rendered him unconscious. He

[1]The polarographic technique while recording changes in oxygen tension during a seizure will not be disturbed by the D.C. potential changes across the cortex which are known to be associated with seizures. (In this laboratory, D.C. shifts between two cortical electrodes of as much as 5 millivolts can be recorded during strychnine or Metrazol seizures. Goldring and O'Leary (1959) have previously demonstrated this.) An analysis of the polarographic electrode system shows that it is primarily a high resistance, constant current electrolytic system. The high resistance (3–8 megohms depending on electrode size) at the surface of the polarized platinum electrode will greatly reduce the significance of any potential located between the recording electrodes. For this reason, changes of D.C. potential of 5 M.V. between the recording electrodes of the polarographic system will be insignificant in disturbing the measurement of current flow (oxygen tension). On the other hand, the capacitance at the polarized electrode is also high (and proportional to electrode size), and for this reason, capacitative recording of the EEG will always be an unavoidable artifact on the polarographic trace (as seen in Meyer's records). Similarly, any changes in the D.C. resistance of the brain during a seizure will not be reflected in the polarographic electrode record, as the changes which occur (a higher impedance during seizures) are insignificant when compared to the constant resistance of several megohms at the platinum-brain interface.

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regained consciousness sometime later in a hospital and was told that he had had a cerebral concussion. Four months later he experienced his first seizure which began with the feeling of dizziness and was then followed by a throbbing sensation in his head, after which he lost consciousness. During this period of loss of awareness, he wept but had no tonic or clonic movements. Following recovery he was groggy and exhausted. Two similar attacks followed in the next months.

At the start of his fourth attack, the patient observed a "tingling" sensation in the toes of his left foot. In subsequent seizures, which began to occur with increasing frequency, he observed that the premonitory tingling which at first was restricted to his toes would spread up his leg. In each succeeding seizure the tingling sensation advanced farther up his leg, then arm, then shoulder before consciousness was lost. Finally, he developed the seizure pattern which has now become stereotyped.

At the present time the patient almost always develops a "pins and needles" feeling in the toes of his left foot at the onset of his seizure. This tingling spreads upwards to involve his leg and his thigh. At the time it has reached the hip, he notices the onset of tingling in the fingers and then the hand on the same side. The tingling then advances up the arm to the shoulder, the left side of the neck and then the face. When the paræsthesias have reached the neck and face, the patient develops adversive movements of the head towards the left and, while these are occurring, he "hears" a non-localized "banging" on his left. This sound resembles that made by pipes banging together. At first the frequency is low and then increases to a crescendo at which point he loses consciousness. On only six occasions has the patient also experienced a formed visual hallucination which occurs at the same time as he "hears" the left-sided banging sound. He "sees" a person standing to his left. On three occasions he "saw" the lieutenant of his army unit dressed in fatigue uniform. On one occasion he "saw" the colonel of his regiment and on one occasion he "saw" a nurse who attended him when he was hospitalized for his head injury. His last visual hallucination was of an unrecognized person. The visual hallucination is exceptionally vivid and appears to him to be exactly like a normal visual experience. Yet he "knows" that the person he sees is not really there.

Three years after his seizures began, he commenced taking 100 mg. Dilantin twice daily but was rather intermittent in his therapy. The dosage was increased to 300 mg. and then to 400 mg. daily, which he has taken regularly. With this increased dosage his seizures were much less frequent but still occurred about twice weekly. On the increased dose of Dilantin, he began to have abortive attacks in which he experienced tingling in the foot, leg and arm which was not followed by unconsciousness. If the paræsthesia reached his shoulder, however, unconsciousness invariably occurred. The patient estimates that approximately 20 per cent of his attacks were abortive.

During his major seizures he becomes flushed and is unresponsive. He may then begin to cry or to crawl on his hands and knees. He occasionally mumbles a word repetitively—the word "ether" being frequently used. On other occasions he is silent, except for weeping. When he regains consciousness, he is confused for a few minutes and complains of a bad taste in his mouth.

Following the seizure he is, at times, quite exhausted and unable to work. At other times he feels capable of working. He has had, on occasion, a very mild weakness of his left leg and arm following his seizure usually lasting for a few minutes but once in a while persisting for as long as an hour or two. The mild weakness appears to be about the same in the arm as in the leg.

Despite daily therapy of 400 mg. Dilantin and 120 mg. phenobarbital, he has continued to have approximately two seizures a week. Because of the stereotyped nature of his seizure and the prolonged duration (1 minute to 5 minutes) of the aura, it was felt that this patient might be able to arrest his seizures by painful stimuli applied to his

left leg in a region ahead of the advancing sensory aura. He was instructed to rub his leg vigorously with a stiff nylon brush as soon as possible after the beginning of the aura.

With the use of the brush, the patient immediately had an increase of the frequency of *arrested* fits. The overall frequency of seizures remained unchanged. While previously only 20–25 per cent of his seizures stopped spontaneously, now over 95 per cent of his seizures stopped before consciousness was lost. Frequently, however, the aura passed through the region of skin which he was brushing, and he would have to begin brushing again, this time higher up on his leg or arm than previously in order to arrest the attack. He had several episodes in which the seizure was not arrested until the paræsthesias had reached the neck and face. The patient observed that previously he had never had an arrested seizure once the aura had reached his neck and the banging sound developed.

In an attempt to arrest seizures earlier in their course, the patient was instructed to use a pin, sticking himself rapidly in a region of the skin just above the advancing aura. This change of the nature of the stimulus has not proved to be significantly more effective in arresting seizures. The use of a ligature above his left knee is no more effective either.

In the seven months that the patient has been using sensory stimuli to arrest his seizures, he has had only five major attacks with loss of consciousness. The first occurred when he had insufficient time to reach the brush which he had left in his coat in a locker room. The second occurred in his sleep and was noted by his wife. The third occurred despite the use of the brush. For an unknown reason the patient did not, on this occasion, continue rubbing his skin after the aura passed the level of his elbow. The fourth attack occurred with such a rapid march of the aura and with a premonitory feeling of intense heat ("as if I had walked into an oven") that he hardly had time to apply the sensory stimulus. The fifth occurred during right carotid arteriography when the patient was unable to apply the stimuli.

The patient spontaneously complained, after he had been arresting seizures by these means, that following arrested seizures he experienced much more severe and prolonged weakness in his arm and leg.

The weakness and clumsiness of his extremities which previously was clinically insignificant and brief became, after arrested attacks, sufficiently severe so that he could scarcely walk or hold anything in his hand. The weakness in his hand occurred, even following those attacks in which the paræsthesia died out in the calf of the leg, no subjective abnormalities having been noted in the arm at any time. In one particular attack, repeated pricking of the skin of the thigh succeeded in containing the paræsthesia to the region below the knee. However, despite this vigorous pricking, the aura persisted in his leg for as long as fifteen minutes before it finally subsided. Following the subsidence of the attack, the patient observed that the arm and hand as well as the leg were exceptionally weak, and this persisted for over twelve hours.

The patient has generally not been able to relate the severity and duration of the postictal paralysis with the severity and duration of the arrested seizures.

On one occasion (after the fourth major seizure in which he had no time to effectively apply the sensory stimulus as the march was so rapid), he was examined within an hour of regaining consciousness. There was very mild weakness of the left arm and leg. The hand was spontaneously held in a partially clenched position with the thumb fully adducted and buried under the fingers and the forearm was flexed and adducted. He did not use the arm spontaneously, but performed well on formal testing of co-ordination and fine movements. There was a minimal hemiplegic gait. No sensory loss was noted and no pathological reflexes were present. Deep tendon reflexes were difficult to elicit but were symmetrical. The patient described these particular difficulties as relatively "mild" and maintained that, after an arrested seizure, the weakness was much more severe. All signs disappeared within a few hours.

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Routine EEG studies were repeatedly normal as were several recordings following the injection of 8 c.c. of a 5 per cent solution of Metrazol. Sleep recordings, however, consistently showed spikes and sharp waves in the right anterior temporal region. Pneumoencephalography revealed that the right temporal horn was slightly higher than that of the left side. Right carotid arteriograms are illustrated in Figs. 1, 2, (Plates XLIV and XLV). The large right-sided arteriovenous malformation also filled following left carotid injection.

Discussion

The effect of the ligature, or other noxious stimulus in arresting seizure activity has been recently reviewed (Efron, 1956, 1957). At that time attention was directed to the appearance of bizarre postictal sequelæ as a consequence of arresting seizures by senory stimuli. This has been reported by many observers.

In this particular case, however, the consequence of arresting seizures was the production of a dense postictal paralysis. The postictal paresis under these conditions was much more severe and more prolonged than when it followed an uninterrupted attack. This is precisely what was reported by Jackson's patient—and it was on this case that Gowers took issue with the Todd-Robertson hypothesis. Of even greater interest, however, is that our patient repeatedly developed a paresis of the arm *following the arrested seizures even when there was no evidence that seizure activity had involved that region of the brain.* This is incompatible with Jackson's statement that the paralysis is more severe, the more severe the convulsion in the part.

This patient had a large A–V malformation which almost certainly is responsible for his seizures. Despite this major vascular anomaly, his post-epileptic paresis was usually minimal, and frequently non-existent. Yet following arrested seizures the paralysis was much more severe.

While admitting that the cerebral circulation might be marginal in one Rolandic region of this patient, it is difficult to conceive of a mechanism by which a sensory stimulus could tip the balance in favour of vascular insufficiency—especially as the same stimulus also results in a shorter seizure and thus a diminished demand for oxygen. The same argument applies, as Gowers saw, against the hypothesis that the nerve centres are "exhausted." Why should they be more "exhausted" following a restricted seizure than a major one and why should the cells of the "arm area" in this case be "exhausted" at all? Similarly, any hypothesis which is based on the accumulation of a known or unknown metabolite would be faced with identical difficulties.

It is at this point that we must return to the nosological problem of the various paralyses which occur in relation to seizures. Tentatively, the "ideal case" of Todd's paralysis could be defined as one in which the patient has had a nonprogressive neurological disease and has suffered from focal seizures for many years. Each of these seizures has been followed by a brief paralysis with complete recovery, no neurological abnormalities ever

PLATE XLIV

FIG. 1.

To illustrate article by Robert Efron.

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PLATE XLV

FIG. 2.

To illustrate article by Robert Efron.

noted except in the few hours following a seizure. No episodes of paralysis, however transient, have occurred which were not preceded by a seizure.

Such criteria have not been explicitly stated by most writers on this subject and, for this reason, it is not surprising that in many of the cases reported, the patient did not have a Todd's paralysis. It is understandable that the early writers (Bravais and Todd) confused cases of "Todd's paralysis" with the paralysis which results from a cerebral thrombosis in which a seizure is associated with the onset of the acute syndrome. The paralysis is frequently brief in these cases and the patient often has a complete recovery. It may be difficult, on the first episode, to distinguish this from "true" post-epileptic paralysis. In these cases, the paralysis is certainly due to cerebral anoxia.

Syndromes of carotid insufficiency, unknown to these 19th century neurologists, with the usual transient paralysis, may be ushered in by a seizure. A number of episodes of cerebral ischæmia may occur, each perhaps with an attendant seizure and each one followed by a rapid and complete return of power of the affected side. In these cases too, the seizure as well as the paralysis are undoubted consequences of transient episodes of cerebral anoxia. Cases of this type have been reported as suffering from Todd's paralysis but, by the present criteria, should not be included within this group. Another class of confusing cases is that in which a progressive cerebral lesion produces what appears to be a transient paralysis, but in which the postictal paralysis does not *quite* disappear. Each succeeding seizure leaves an increasing residue of paralysis until a complete hemiplegia results.

An even more complicated case is that of James Collier (1928) who described a 37-year-old woman who had only generalized nocturnal seizures for twenty years. She then had

"an attack of local convulsion in the right hand without any impairment of consciousness, and this was followed by other attacks of like nature with increasing frequency, until when I first saw her she was having attacks at regular intervals of 20 minutes night and day, and in this condition she was admitted into the National Hospital. The attacks commenced by the patient calling out that she had 'horrible pain' in the right-hand which showed slight tonic spasm followed by clonic spasm of no great intensity, which lasted some three minutes. The spasms spread slowly up the arm, but never higher than to cause a partial involvement of the deltoid with slight abduction at the shoulder. Never did the convulsion spread to the face, tongue, trunk or lower extremity. Nor was there any loss of consciousness nor aphasia. There were never at any time any signs of raised intracranial pressure, nor were there any objective disturbances of sensibility, even in the right hand. . . . In a little while, with the regular continuance of the attacks, it was noticed that the hand and arm were weak between the attacks, and then were completely paralysed between the attacks; the paralysis spread slowly to the tongue and face, but there was never the least trace of aphasia, and it spread also to the leg, foot first. In the course of a fortnight this patient had developed an absolute and stony hemiplegia with all the signs of pyramidal involvement well marked, notwithstanding that there had never been the least sign of convulsion either in face, tongue or leg. So far as these regions were concerned, the condition was one

of simple epileptic paralysis as the isolated result of the epileptic attacks. Some little time later the attacks suddenly ceased and thereafter the paralysis of tongue, face, leg and arm, in that order, lessened and completely disappeared, the abdominal reflexes returned, and even the extensor response in the plantar reflex had changed to normal by the time she left the hospital six weeks after her admission. Six years later, just before Christmas of last year, this patient walked into my consulting room. She had had three fits in the six years of her old, general, nocturnal type. She had recently had a fit in the daytime, commencing in the right hand and followed by weakness, and come to me in fear of a repetition of the events of 1922. I found that she had for some months been dragging the right leg in walking and there was a definite extensor response in the right plantar reflex. Some extension is now occurring from her local lesion."

This case of Collier's illustrates that patients with progressive cerebral lesions may also have episodes of "true" Todd's paralysis, and that the paralysis may affect regions of the body which were not involved in the fit.

The classification of paralysis associated with seizures, which has so far been relatively simple, becomes exceedingly difficult (and in the author's opinion meaningless) when the post-epileptic paralysis has to be differentiated from the paralyses of "inhibitory epilepsy." In inhibitory epilepsy one conceives of a sudden arrest of function (paralysis) as the *only* manifestation of the fit. These cases are not common. Sometimes there are bizarre mixtures of "inhibitory" and "excitatory" phenomena. In these cases there are as yet no criteria by which the inhibitory phenomena can be differentiated from postictal paralysis.

Gordon Holmes (1927) refers to a case of Jackson's in which "clonic movements of the face were immediately followed by paralysis of the hand of the same side." Holmes went on to report a case of his own in which focal Jacksonian fits were followed by postictal paralysis of the right fingers and wrist. "Sometimes, however, attacks occurred in which there were neither tonic nor clonic spasms . . . he simply lost power suddenly and without any warning in the hand . . . The loss of power was complete for a time but after a few minutes voluntary movements returned and gradually reached the normal."

Penfield and Jasper (1954) report a post-operative case in which

"the convulsive movement affected the contralateral (left) face. But the eyes deviated to the right, and there was also a flaccid paralysis of the left arm and partial paralysis of the left leg as well. Neither arm nor leg showed convulsive movements at any time. Between seizures these paralyses cleared up. After each seizure there was paralysis of the left face which cleared up quickly but outlasted the paralysis of the arm. The whole condition disappeared after the seventh post-operative day and his convalescence was uneventful."

Penfield and Jasper attributed the paralysis of the left arm, as well as the conjugate deviation to "inhibitory paralysis" as they occurred *during* the seizure, but attributed the facial palsy to the "usual postictal or Todd's paralysis which ordinarily affects the part most involved in movement during the seizure."

The implicit distinction which Penfield and Jasper made between "in-

hibitory" and "postictal" paralyses (it is the same distinction which Jackson and Clark tried to make), if applied to the case reported in this paper, would mean that the paralysis of the arm following seizures which were arrested in the leg would have to be called "inhibitory," while the *same* type of paralysis, in the *same* region, after a complete seizure would then be called a "post-epileptic paralysis." The distinction between these two phenomena thus appears to be artificial. It is because Gowers rejected this distinction that he then rejected the Todd-Robertson hypothesis.

The Todd-Robertson hypothesis has been demonstrated to run into insurmountable difficulties on both clinical as well as experimental grounds, but the rival theory of Gowers never defines "inhibition" with precision. Recent work on the mammalian spinal cord has pointed strongly to the idea that, on a cellular level, inhibition is often associated with hyperpolarization of the cell membrane. This has been extended to the cortex by Phillips (1956*a*, 1956*b*). Extensive physiological studies have been summarized by Eccles (1957) which strongly suggest that the "final common path" for many inhibitory mechanisms in the spinal cord is the release of a hyperpolarizing neural transmitter by an interneurone. If such a mechanism (demonstrated only in the spinal cord) also exists in the cerebral cortex, it might be expected that hyperpolarization of single cortical neurones will occur at the time of the termination of a seizure. Such intracellular studies on the intact cortex are at the very limit of what is presently technically feasible and for this reason, little information has been adduced to support the hypothesis that seizures are terminated by such inhibitory mechanisms. The author (1961) has succeeded in recording the membrane potential of two cells in the motor cortex of a cat during induced convulsions. In both cases, a marked hyperpolarization developed during the tonic phase, increased further in the clonic phase, and was highest still in the immediate post-clonic period. It slowly returned to the pre-ictal level during the recovery phase following the fit. While these data are by no means sufficient to "prove" any hypothesis, they do, at least, suggest that hyperpolarizing mechanisms are active during seizure states and that their activity might well be responsible for the production of the postictal paralysis as Gowers predicted.

Summary

(1) Todd's thesis that the post-epileptic paralysis is due to "exhaustion" of the neural centres has been reviewed. No evidence supporting this idea withstands critical analysis.

(2) The more recent explanations that the postictal paralysis is due to anoxia similarly fail to account for the clinical phenomena. The experimental work purporting to substantiate this view is inconclusive and misleading.

(3) Both theories fail to explain why postictal paralysis is sometimes

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worse following arrested or partial seizures than it is after complete seizures.

(4) The distinction between postictal paralysis and ictal paralysis (inhibitory epilepsy) is arbitrary and leads to confusion.

(5) A unique case has been presented which illustrates the difficulties in the prevailing theories.

(6) Gowers' thesis that most of the phenomena of postictal paresis are best explained by an active inhibitory mechanism has been reviewed and recent experiments tending to support his idea have been described.

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CRISES IN POST-ENCEPHALITIC PARKINSONISM

BY

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THERE is some evidence that epidemics of encephalitis lethargica occurred in Europe in the seventeenth and eighteenth centuries. The most notable outbreak of this disease, however, was in the later part of the nineteenth century: it became pandemic from about 1917 and reached its peak about 1920.

J. P. Albreit was probably the first writer on this subject to report on a case of oculogyric crisis. In 1695 he reported the case of a girl of 20 who had typical symptoms of encephalitis lethargica and who subsequently developed episodic upward rolling of the eyes.

Most of the early writings on oculogyric crises occurring as a sequel to this pandemic of encephalitis lethargica came from Western Europe (Lévy, 1922; Fischer, 1924; and Meyer, 1924). Cases of oculogyric crises were not reported from North America until 1925 (Hohman, 1925); reports from this country appeared much later. Duncan (1924), in a comprehensive account of the sequelæ to encephalitis lethargica made no reference to crises. From 1926, however, a number of reports appeared (Barkas, 1926; Bramwell, 1928; and McCowan and Cook, 1928).

In individual cases of post-encephalitic Parkinsonism the disability and distress caused by crises may in fact be much greater than that resulting from tremor and rigidity. Some patients with minimal tremor and rigidity experience severe crises lasting for twelve hours or more and these sometimes occur as often as three times a week. A general practitioner who suffered from post-encephalitic Parkinsonism, writing on his disabilities (*Lancet*, 1948), regarded sialorrhœa as his greatest tribulation—in spite of the fact that he had marked rigidity and was able to type with only one finger.

The present study is concerned with 67 patients with post-encephalitic syndromes. They have been cared for at Stobhill General Hospital, Glasgow, for periods varying from six to thirty years. There are 32 men and 35 women. In 27 of these patients (10 men and 17 women) crises

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punctuate the course of the disease; a patient may have more than one type of crisis. Personal observations were carried out at all stages of these crises. Various phenomena were noted systematically; ocular deviation, size and reaction of the pupils, severity of tremor and rigidity, sialorrhœa, blood pressure, heart-rate, the occurrence of flushing of the face and conjunctiva, sweating and the amount of noise (e.g. moaning or howling) made by the patient.

Clinically three types of crisis have been observed in post-encephalitic Parkinsonism: first, the classic oculogyric crisis; a second type in which various manifestations of disturbance in the autonomic nervous system—particularly sweating—are the main characteristics; and third, respiratory or "breath-holding" crisis. Table I gives the frequency of these three types of crisis.

TABLE I.—FREQUENCY OF VARIOUS TYPES OF CRISIS IN POSTENCEPHALITIC PARKINSONISM

TYPE OF CRISES.	NO. OF MALES.	% OF TOTAL NO. OF MALE PATIENTS.	NO. OF FEMALES.	% OF TOTAL NO. OF FEMALE PATIENTS.	% FOR BOTH SEXES COMBINED.
OCULOGYRIC	6	20%	I4	40%	29.8%
SWEATING	5	I5.9%	3	8.5%	II.9%
RESPIRATORY OR BREATH-HOLDING ATTACKS	-	-	I	2.8%	I.5%

OCULOGYRIC CRISES

These patients have had oculogyric crises of all degrees of severity and occurring at intervals varying from a few days to several months. The most severe forms of oculogyric crises occur much more frequently in women than in men. There is also a higher incidence and frequency of crises in general among women patients. An individual patient may have crises which are sometimes severe and sometimes only mild.

Prodromal Stage

Nurses who have had long experience in the care of post-encephalitics can often foretell the onset of an oculogyric crisis. The patient who has been ambulant feels less inclined to leave his bed; or if he is up he is slower in his movements and gait. There is a tendency for the conjunctivæ to be a little injected at this stage.

Emotional changes are common. Some patients become more quarrelsome for a day or two before a crisis. Others are depressed for some hours before the crisis. Some experience an aura before the crisis develops: the sensation is evidently unpleasant and even fearful, but descriptions are

vague. One patient breaks out with repetitive and apparently meaningless jargon shortly before the actual rotation of the eyes. All have a preoccupied staring expression just before the ocular movements occur. Nystagmoid movements may be observed at this point; and in a few patients the appearance of the eyes and a state of fear combine to produce a facial expression of terror.

The Stage of Tonic Deviation or Rotation of the Eyes

The eyes are usually rotated directly upwards but sometimes upwards and laterally, and in 2 patients in this series the eyes are sometimes rotated downwards. The direction of rotation is nearly always constant for each patient, but on occasion upward rotation alone is present in a patient who usually has upward and lateral movement. It is of interest to note that when lateral movement of the eyes is present, the eyes are usually directed away from the side of the body showing the greater degree of muscular rigidity. Skew movements of the eyes have been observed in one patient during some attacks. In a few patients the direction of rotation of the eyes varies even in the same episode. The eyes are usually open and the patient has a fixed stare. 3 patients, however, suffer from photophobia and this causes them to keep the eyes tightly closed. They tend to lie on one side and try to pull the bedclothes over their eyes. 2 patients occasionally experience drooping of the eyelids and cannot voluntarily open the eyes.

In the fully established oculogyric crisis the eyes are fixed. Just before this stage is reached, a well-marked vertical nystagmus with the quick component movement upwards is often observed. There is usually an associated flickering movement of the upper eyelids.

At the fully established stage voluntary horizontal conjugate movement of the eyes is either impossible or, if it can be executed, is only momentary. Voluntary movement of the eyes downwards is usually impossible. If a patient has been persuaded to move the eyes into the horizontal or downward position, it is characteristic that upward conjugate deviation is restored by a very sudden movement of the eyeballs. Congestion of the scleral conjunctiva is also obvious during an oculogyric crisis. In the fully developed case engorgement of the vessels may be extreme: sometimes a large number of dilated capillary vessels are visible in either the lateral or medial limbus or both (*see* figs. 1 and 2, Plate XLVI). In most cases of severe crisis excessive lachrymation is obvious, and there is then occasional escape of tears from the eyelids.

During an oculogyric crisis the pupils are usually dilated, although fixed small pupils have been noted in one patient. Reaction to light is characteristically sluggish. As convergence is rarely possible, reaction to accommodation can rarely be determined satisfactorily.

During the crisis facial flushing is always present and slight congestion

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of the skin may occur as part of the prodromal syndrome. The head is tilted so that usually the occiput and the eyeballs move in the same clockwise direction. Sometimes there is also head retraction. The skin of the forehead may or may not be wrinkled. Muscular rigidity is often increased. Tremor may become more marked; but patients with slight tremor may lose it altogether during an oculogyric crisis—perhaps because the movements are eliminated by the state of increased muscle tonus. A remarkable phenomenon is the obvious unwillingness to move (bradykinesia) and sometimes immobility is absolute (akinesia). The patient abandons the struggle to move his limbs; the whole body is extremely rigid and he has to be moved like a tailor's dummy. When they are in the throes of an oculogyric crisis the majority of patients are unable to feed themselves; but if food is put into the mouth patients show little difficulty with mastication or deglutition.

Vertigo, objective or subjective in type, is complained of by 8 out of 20 patients during crises. Headache—usually frontal, but rarely occipital—is a common complaint but it is not incapacitating.

Increased salivation is seen in less than one-half of the patients and in these it is inconstant. The blood pressure may be raised by as much as 60 mm.Hg systolic and 30 mm.Hg diastolic; tachycardia is common and is not constantly related to change in blood pressure. Irregular respiration is seen in a few patients; tachypnœa is followed by variable periods of apnœa.

Emotional disturbances occur in all severe cases. Despite rigidity and immobility during the crisis, these patients are rarely silent; grunting, mumbling, moaning or howling are commonplace; and some emit sudden squawking sounds—which one resident medical officer described as being like the plaintive cry of a seagull. The noise is sometimes loud enough to be audible more than 200 yards away. The patients cannot explain why they shout or moan. 3 patients are invariably quiet during crises, and it is noteworthy that in these patients flushing of the face is trifling or absent altogether. Some patients repeat particular words or sentences—but these convey little or nothing to the observer. The patients described their feelings as being "terrible," and it is evident that they are in a state of fear. During a crisis one patient sometimes has outbursts of uncontrollable laughter. Hallucinations have never been detected. Incontinence of urine was seen occasionally during oculogyric crisis.

Sweating Crisis

The post-encephalitics in this series have revealed intolerance for warmth as compared with normal people. They tend to sweat much more easily and prefer the cold weather to hot weather.

Eight patients have paroxysmal attacks of excessive sweating even in the winter months. The phenomenon is so sharply defined and so com-

pletely independent of environment, that it has been designated a "sweating crisis." 5 of these patients are men and 3 are women (*see* Table I). 4 of them have severe attacks periodically. 2 patients (1 man and 1 woman) display both oculogyric and sweating crises; and these two types of crisis may occur simultaneously or at different times.

The crises can occur at any time but are much more frequent late at night or early in the day. During the crisis, severe tremor is commonly present but it is thought that only occasionally is the increased muscular activity an important factor accounting for sweating. Sweating is so profuse that it may necessitate a change of garments and bedclothes once, or more often, in an hour; and this has occurred in the absence of any marked increase in the degree of tremor beyond that normally present. Further, in one patient where oculogyric crisis is associated with the development of severe tremor, sweating is not excessive. In a sweating crisis there is usually flushing of the face and sometimes congestion of the conjunctiva. The skin of the limbs may also be hyperæmic. The axillary temperature may exceed 100° F.

One patient whose tongue normally shows marked tremor, makes clicking noises during a sweating crisis by alternately protruding and partially withdrawing the tongue. Severe cyanosis has been seen in this patient during sweating crises. This is attributed to mechanical obstruction: there is marked forward flexion of the neck and because the tongue is often extruded, breathing through the mouth is made more difficult. Increased oxygen utilization from excessive tremor may also be a minor contributory factor.

There is severe tachycardia during a sweating crisis: the heart-rate may reach 150/min. The cardiac rhythm is usually regular but very rarely extrasystoles occur. The systolic blood pressure rises by 20–50 mm.Hg and the diastolic pressure by about 20 mm.Hg. Excessive salivation is frequently seen.

Illustrative Cases

Case 1.—Woman aged 56. This patient was admitted in 1946. No history of a febrile illness resembling encephalitis lethargica could be elicited. She had gone to Australia in 1926 and two years later, following a tonsillectomy, she found that she had muscular weakness on one side of the body and tremor on the other. She returned to the United Kingdom and was eventually admitted to Stobhill General Hospital. Oculogyric crises began in 1942.

On examination at the time of admission she was described as a thin woman with mask-like facies. She had typical Parkinsonian tremor affecting the limbs, head, tongue and eyelids. There was some loss of muscular power with wasting. Speech was toneless. She seemed to be of average intelligence and had a fairly good memory. Deep reflexes were normal; plantar responses were flexor. Examination of other systems revealed no abnormality except a systolic hypertension; B.P. 170/86.

Examination in 1959 confirmed the former findings. There was moderate hypertonicity of all limbs, more marked in the left arm. Muscle power in the right arm was fairly good but was diminished in other limbs. The pupils were small, reacting to light

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but not to accommodation; there was slight weakness of the right lateral rectus muscle. Blood pressure 170/90 mm.Hg; pulse-rate 80/min.

Treatment.—In 1950 she was placed on benzhexol ("Artane") 20 mg. daily but in 1953 it was withdrawn owing to unbearable side effects and she was placed on tincture of strammonium 2 ml. daily.

Comment on present condition (1960).—She suffers from very severe oculogyric crises which, if untreated, may last up to twenty-four hours. Sweating is sometimes excessive but does not compare with that of a severe sweating crisis. The blood pressure usually rises (the systolic pressure by 10–40 mm.Hg and the diastolic pressure by 10–30 mm.Hg); the systolic pressure may exceed 200 mm.Hg, and some of these occasions mild epistaxis has occurred. The heart-rate rises by 10–20 beats per minute. In some crises there is vertigo, and if the patient is sitting up she then shows a tendency to fall to one side.

Case 2.—Woman aged 40, admitted in 1944. She gave a history of having had "sleeping sickness" at the age of 7. Some years later she developed stiffness of both lower limbs with some difficulty in walking.

On examination at the time of admission she was found to be well nourished but not very intelligent. She had increased muscle tone and tremor in all limbs. The pupils were equal and of normal size, reacting to light and accommodation. The tendon reflexes were exaggerated. Examination of other systems revealed no abnormality. *Oculogyric crisis* was first noted in June, 1949, about twenty-two years after the attack of encephalitis lethargica.

Examination in 1959 showed no deterioration. Rigidity and tremor were, however, almost entirely confined to the left side. The pupils were normal in size and shape, and reacted to light and accommodation. She had a festinant gait. Speech was slow and monotonous. The reflexes were normal apart from moderate increase in the knee-jerks. The blood pressure was 130/90; pulse-rate 90–100/min.

Treatment.—She had been treated originally with tincture of strammonium but from 1950 she received benzhexol 10 mg. thrice daily.

Comment.—The patient has frequent oculogyric crises—up to three per week. If treatment is not adequate a crisis may last six to twelve hours. They may be precipitated by emotional upset or by annoyance. During the crisis the eyes are rotated upwards and to the right. The blood pressure does not rise significantly, but the heart-rate may rise by as much as 20 beats per minute.

Case 3.—This man, aged 50, was first admitted to Stobhill General Hospital in 1933, following a "fit" in the street. The history was obtained from his wife. At the age of 14 (about 1924) the patient "suffered from sleeping sickness," and received treatment in hospital. Subsequently he appears to have been completely free from symptoms for seven years: the post-encephalitic syndrome began in 1933—about two and a half years before his first admission to Stobhill General Hospital. He complained of tremor affecting the right side. The disability was progressive: dysarthria developed and hypersalivation became troublesome.

The clinical notes at the time of admission refer to a marked tremor affecting the left arm and leg. The pupils were then irregular and did not react to light or accommodation. He was sweating excessively.

He was discharged in 1934 but was readmitted shortly afterwards. At this time it was noted that he had an expressionless face and marked tremor of all limbs, but the face and tongue were not involved. He was again noted to be sweating profusely. Reflexes were normal. Examination of the other systems showed no abnormality.

Examination in 1959 showed deterioration. He was now bedridden with flexion

deformity at both knees. Tremor was present in all limbs, and also in the lips, jaw and tongue. Ptyalism was still present. He was unable to feed himself and had some difficulty in swallowing. His speech was very indistinct. Muscle tone was moderately increased, especially on the left side; muscle power was generally poor. There was dissociation of eye movement although there was no definite palsy of extrinsic ocular muscle. His blood pressure was 110/70 mm.Hg and the pulse-rate 72–80/min.

Treatment.—He was originally treated with strammonium-hyoscine mixture but benzhexol was substituted in 1950.

Comment.—Despite receiving benzhexol, 15 mg. daily, sweating crises are frequent. Some are very severe, requiring a change of garment and bedclothes three times in one hour. He does not have oculogyric crises. The rise in systolic and diastolic pressures during severe attacks is up to 50 mm.Hg and 20 mm.Hg respectively. The degree of tachycardia also varies but on one occasion the cardiac rate was over 150/min. Commonly the cardiac rate is between 120–136/min.

Case 4.—A woman aged 56. She was admitted to Stobhill General Hospital in December 1948. She had been well until the age of 24 (1928) when she developed "sleepy sickness": she was treated at home. Shortly after the acute phase, she noticed tremor of the left hand, and later of the right hand. Six years after the acute phase of encephalitis lethargica she began to have oculogyric crises. These episodes occurred about twice a week and lasted some twenty-four hours. During a crisis she felt as if she were going to fall, or that objects in the room were rotating round her. She continually had double vision with one image above the other, but during the oculogyric crisis diplopia was much worse. She managed to do her housework until four years before her admission to hosp'tal.

On examination at the time of admission (1948) she was reported to be a well-built woman with tremor of the hands and tongue. She had a sluggish speech and moderate deformity of the limbs. The pupils were normal in size and reacted to light and accommodation. The deep reflexes were normal and the plantar responses were flexor. The other systems showed no abnormality.

Examination in 1959 confirmed the findings of 1948 but the rigidity was mainly left-sided. The tendon reflexes were exaggerated but the plantar reflexes were flexor. The blood pressure was 160/90; pulse-rate 70/min.

Treatment.—She had been receiving benzhexol 20 mg. daily since 1953.

Comment.—Her crises are not now as frequent as they were, but their severity has not diminished. During a crisis she repeats endlessly a meaningless formula of words. The eyelids may droop and she is unable to open her eyes voluntarily (she raises the upper lid with her fingers). Superficial vasodilatation is very obvious: large numbers of distended capillaries are visible in the scleral conjunctiva. She is not noisy (no shouting) but is often very weepy. The blood pressure during crisis may rise and is sometimes as high as 204/110; and the cardiac rate may increase to 120/min.

Pathogenesis of Oculogyric Crisis

Various theories as to the pathogenesis of oculogyric crisis have been formulated. It has even been suggested that the tonic deviation of the eyes is a hysterical manifestation. Two theories will, however, be discussed in detail.

(1) *The Relaxation-Sleep Mechanism Theory of Hall*

Hall (1931) in his Schorstein Lecture drew attention to the sequence of

events when the normal person closes his eyes: when the lids make contact the eyeballs roll upwards. He noted that sleep relieved the crises. He also stated that there is absence of wrinkling of the forehead during an oculogyric crisis. Hall considered that these observations suggested that upward rotation of the eyes is due to a sleep mechanism. However, not infrequently, wrinkling of the forehead is seen in patients in oculogyric crisis. Further, in patients with post-encephalitic Parkinsonism, the absence of wrinkling may be continuous: it is then probably associated with rigidity of the occipito-frontalis muscle (fig. 3). There is a suggestion that failure of the eyelids to close when the eyeballs roll upwards causes distress. This, however, is not true, as a number of our patients sleep with their eyes partially open and the eyeballs rolled upwards. Further, in one patient there is a stage during oculogyric crisis when marked drooping of the upper eyelids occurs, and this is accompanied by increased distress. The beneficial effect of natural or drug-induced sleep is to be attributed to the rest afforded to the active parts of the nervous system and to the body as a whole.

(2) *The Compulsive Obsessive Theory of Jelliffe*

Jelliffe (1929) suggested that an oculogyric crisis is a manifestation of compulsive obsessive neurosis. He tried to show that some mental or emotional trauma was essential for the initial onset of oculogyric crisis. The rotation of the eyes and the shouting were regarded as ritualistic and secondary to a repressed feeling—usually of guilt.

Jelliffe's theory seems to be widely accepted (Curran and Partridge, 1955). There is no doubt that the tonic rotation of the eyes and the associated phenomena cannot be controlled by the patients, and therefore in the ordinary sense they are compulsive. There is, however, no evidence that the motor phenomena are ritualistic, nor is there proof of association with repressed feeling of guilt. This theory does not explain why oculogyric crises developed in the series of post-encephalitics under our care. Most of our patients can still remember the first episode and they do not associate its genesis with mental or psychological trauma. Stogdill (1934) criticized the psychoanalyst's view that neurosis is due to energized ideas repressed into consciousness. He showed how an irrelevant stimulus can be associated with neurotic behaviour and stressed the fact that neurotic behaviour, far from being a ritual, is behaviour that has been learnt.

Apart from encephalitis lethargica, Parkinsonism may be due to a variety of causes such as arteriosclerosis, carbon monoxide or manganese poisoning, syphilis, hepatolenticular degeneration, or it may be due to idiopathic paralysis agitans. It is significant that the oculogyric crisis occurs in post-encephalitic Parkinsonism. It was thought that oculogyric crises also occurred in patients with Parkinsonism associated with

cerebral syphilis. Pearson (1927), however, reviewed the cases reported; he showed that in all such reported cases (including the single case record which he had published) there was always an initial illness which was not unlike encephalitis lethargica. He therefore concluded that oculogyric crises in such patients had been the sequel to previous attacks of encephalitis lethargica, and that the concomitant syphilis had had no influence in the pathogenesis of the crises.

Recently, however, "oculogyric crises" have been reported following the administration of drugs of the phenothiazine group (Montgomery and Sutherland, 1959; Davies, 1959; Bickerstaff and Jacoby, 1960). This type of oculogyric crisis is, however, different from the Parkinsonian form in that spasm of the neck muscles with head rotation—and even opisthotonos—is very common and usually precedes upward eye rotation by up to 30 minutes. Faulkner and Hyde (1958) have shown that electrical stimulation of the mid-brain in experimental animals can cause conjugate deviation or rotatory movements of the eyes associated with opisthotonic movements. It may be therefore that these drugs produce similar effects by actions on the same zones of the mid-brain. It should be noted, however, that oculogyric crises have not been seen in patients with drug-induced Parkinsonism.

Why then is oculogyric crisis confined to post-encephalitic Parkinsonism? Pathological studies (McAlpine, 1926) and others have shown that although the inflammatory process may be widespread and involving the cerebrum, the mid-brain and pons bear the brunt of the disease. The most significant pathological changes are the degenerative ones in the substantia nigra. In the other forms of Parkinsonism the lentiform nucleus bears the brunt of the disease process.

Clinically palsy of the third, sixth and seventh cranial nerves are frequently seen in post-encephalitic Parkinsonism. Palsies of these nerves from the mid-brain and pons are very rare in the other types of Parkinsonism. One may therefore conclude that an important difference between the two forms of Parkinsonism (post-encephalitic and non-post-encephalitic) is that the former is primarily due to an upper brain-stem lesion while the latter is due to lesions in the lentiform nucleus.

Recently Shanzer and Bender (1959) studied the effect of brain-stem lesions on oculomotor response to caloric stimulation and found that defects in nystagmus and tonic deviation of the eyes occurred as compared with the response in the normal animal. They found, for instance, that in a monkey with a superior brain-stem lesion on one side there was a defect in tonic deviation of the eyes to the side opposite to the side of the lesion. They also found that, on bilateral caloric stimulation, only upward tonic deviation of the eyes occurred and nystagmus, when present, had its fast component upwards. This oculomotor response is not unlike the tonic eye movements and nystagmus seen during oculogyric crises.

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The effect of mid-brain lesions on muscle tone has been widely studied in experimental animals. Mettler and Zimmerman (1943) found that in cats lesions above the level of the red nucleus gave rise to contralateral rigidity, while ipsilateral rigidity was produced by lesions of the tegmentum below this nucleus. Hardy and Stevenson (1957) reported a case of unilateral syringomesencephalia involving the substantia nigra. This patient had signs of Parkinsonism on the contralateral side. Our observations on this series of patients show that in a majority of cases, where a predominant unilateral rigidity and lesion of the nerves to the extrinsic ocular muscles are present in the same patient, the cranial nerve lesion is on the contralateral side to the rigidity. This explains why when upward and *lateral* conjugate deviation of the eyes occurs in oculogyric crisis, the direction of movement of the eyes is usually *away* from the more rigid side of the body. Thus if the patient's right side is more rigid than the left side, in an oculogyric crisis with upward and lateral movements the resultant deviation of the ocular axes will be to the left side.

A previous study of post-encephalitic Parkinsonism was carried out by Crow in 1949 working in this hospital. About 60 per cent of the patients who are now in the "post-encephalitic wards" were included in Crow's series (Crow, 1949). He reported on the effect of various afferent stimuli (such as spraying of the side of the neck with ethyl alcohol, sniffing strong ammonia and caloric vestibular stimulation) on eye movements in patients suffering from post-encephalitic Parkinsonism. He found that he was able to induce oculogyric crisis only by caloric vestibular stimulation.

Study of the various ocular abnormalities in this series of patients shows that 75 per cent of the 20 patients suffering from oculogyric crisis have nystagmus; but of the 40 patients who have neither oculogyric nor sweating

TABLE II.—RELATIVE INCIDENCE OF VERTIGO, NYSTAGMUS AND OTHER OCULAR LESIONS IN THE VARIOUS GROUPS OF THE 67 PATIENTS

GROUPS OF PATIENTS	TOTAL NUMBER	NUMBER OF PATIENTS WITH			
		NYSTAGMUS	VERTIGO	WEAKNESS OR PARALYSIS OF EXTRINSIC EYE MUSCLE	RECENT DIPLOPIA
OCULOGYRIC CRISIS	20	15	8	5	6
SWEATING CRISIS	8	2	0	5	3
WITHOUT OCULOGYRIC OR SWEATING CRISES	40	2	0	5	2

crises only 5 per cent have nystagmus (Table II). In the group with oculogyric crises nystagmus was ordinarily present in 9 of the 20 patients (45 per cent), and this was increased to 15 (75 per cent) when the patients were observed during crises (fig. 4). True vertigo was complained of by

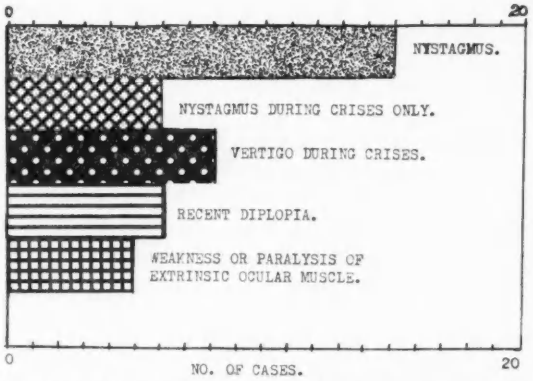

FIG. 4.—The relationship between vertigo and certain abnormalities of ocular movement in 20 patients with oculogyric crises.

8 of the 20 patients (40 per cent) during attacks of oculogyric crisis. The vertigo took various forms, for example, a tendency to fall to one side, apparent rotation of objects, and the sensation of seeing the floor advance towards the patient. No case of true vertigo was seen in the other two groups of patients. Dizziness in the ordinary sense was, however, fairly evenly distributed in the three groups. Crow was unable to correlate liability to oculogyric crises and the presence of nystagmus. However, this may be attributable to the fact that his criteria for the diagnosis of oculogyric crisis differed from the criteria adopted by the present writer: Crow includes patients who showed *staring* without deviation of the ocular axes. Again in the earlier paper, no account is taken of the fact that patients normally free from nystagmus may show this abnormality during oculogyric crises.

There is no evidence of cerebellar dysfunction in these patients. In view of the prevalence of nystagmus in these patients with oculogyric crisis and the presence of vertigo in a fair proportion during oculogyric crisis, one may therefore conclude that the vestibular apparatus (with special reference to its pathway and connexions in the brain-stem) is involved in these patients with oculogyric crises.

Examination of the auditory canals in the whole series revealed that 40 of the 67 patients had grossly excessive quantities of hard wax completely blocking one or both ears. The findings on auriscopic examination

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appeared to be of considerable importance when reviewed in relation to the total clinical picture. It is of interest to note that most of the patients with little or no wax in their ears are those with minimal signs of Parkinsonism or had perforated eardrums (*see* Tables III and IV). It would appear therefore that the findings of a greatly increased secretion of wax in the auditory meatus is associated with post-encephalitic Parkinsonism. This is not entirely unexpected: seborrhœa and a greasy skin are characteristic of this condition (Denny-Brown, 1946; and MacKenzie, 1927) and it may be that increased activity of the sebaceous glands of the skin is paralleled by an increase in the secretion of wax. It is suggested that the persistence of a gross excess of hard wax in the auditory canals is a likely source of vestibular stimulation capable of inducing oculogyric crises in patients with suitable brain-stem lesion.

In 4 patients an attempt was made to determine the therapeutic value of removing wax from the auditory canals. The wax was first softened with "Cerumol" and it was then dislodged by syringing. During the following eight weeks there was no significant reduction in the number of oculogyric crises in these patients, but in one of them the severity of the crises was appreciably diminished.

It would appear that at least two factors are essential before oculogyric crisis can occur, viz.:

(1) *The existence of a particular type of lesion of the brain-stem* which produces nystagmus without evidence of cerebellar dysfunction. Such a lesion is probably an irritative one situated in the vestibular pathway.

(2) *Some source of vestibular stimulation* such as the presence of hard wax in the external auditory canals in sufficient amounts to cause obstruction to the lumen and tension in the walls of the canals. Other sources of vestibular stimulation, such as revolving while waltzing are capable of precipitating an oculogyric crisis (McCowan and Cook, 1928).

That the brain-stem, especially the mid-brain, contains intrinsic co-ordinating mechanisms capable of producing conjugate eye movements, has been observed by various workers and this has recently been confirmed by Hyde and Eliasson (1957) and Faulkner and Hyde (1958). Szentagothai (1950) has shown that there are numerous connexions between the labyrinth and the extrinsic ocular muscles,

The time-interval between the acute illness of the encephalitis lethargica and the onset of oculogyric crisis is very variable; it may be a few years or as long as twenty-two years. The explanation may lie in circumstances which in turn depend upon the different factors concerned in the pathogenesis of oculogyric crises and to which reference has been made above. Although reactivation of the infective process is denied by various workers (MacKenzie, 1927); McPhater, 1942), there is no doubt that the disease may be progressive and that it may extend in the upper brain stem and involve zones and tracts that were not originally involved.

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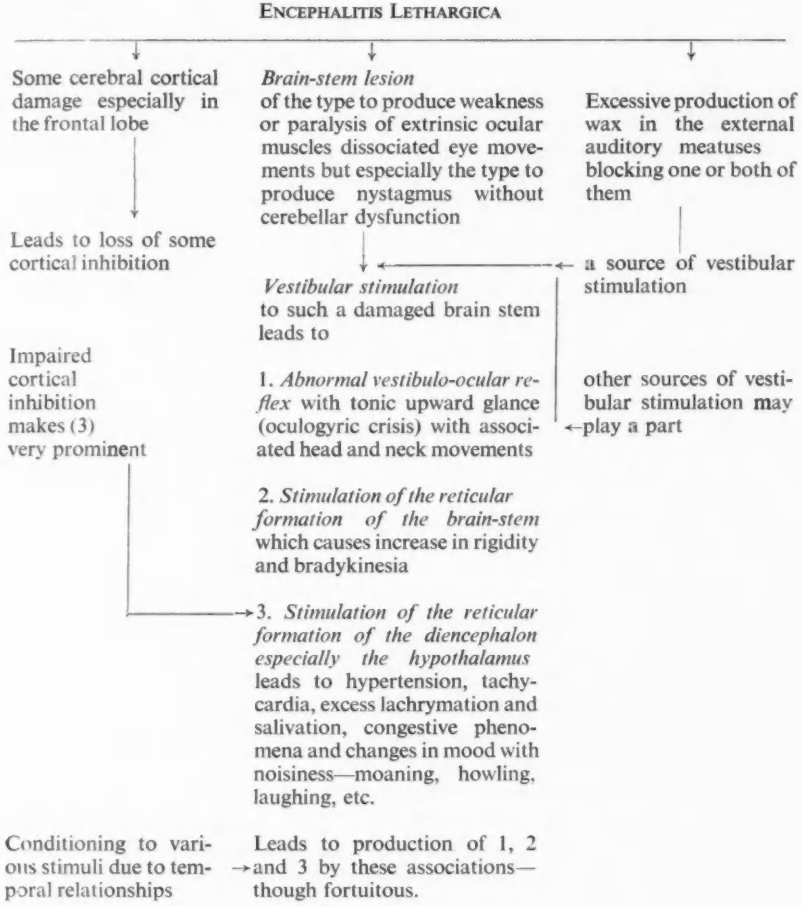
ENCEPHALITIS LETHARGICA
Some cerebral cortical damage especially in the frontal lobe
Leads to loss of some cortical inhibition
Impaired cortical inhibition makes (3) very prominent
Conditioning to various stimuli due to temporal relationships
Brain-stem lesion of the type to produce weakness or paralysis of extrinsic ocular muscles dissociated eye movements but especially the type to produce nystagmus without cerebellar dysfunction
Vestibular stimulation to such a damaged brain stem leads to
1. Abnormal vestibulo-ocular reflex with tonic upward glance (oculogyric crisis) with associated head and neck movements
2. Stimulation of the reticular formation of the brain-stem which causes increase in rigidity and bradykinesia
3. Stimulation of the reticular formation of the diencephalon especially the hypothalamus leads to hypertension, tachycardia, excess lachrymation and salivation, congestive phenomena and changes in mood with noisiness—moaning, howling, laughing, etc.
Leads to production of 1, 2 and 3 by these associations—though fortuitous.
Excessive production of wax in the external auditory meatuses blocking one or both of them
a source of vestibular stimulation
other sources of vestibular stimulation may play a part

FIG. 5.—To illustrate the pathogenesis of oculogyric crises and associated phenomena

THE ROLE OF EMOTION IN PRECIPITATING OCULOGYRIC CRISES

The effect of emotion as a precipitating factor has been observed in this series of patients, and the conclusions are similar to those of previous workers (Bramwell, 1928; McCowan and Cook, 1928).

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In analysing the factors concerned in the pathogenesis of oculogyric crises a distinction must be made between the initial phase and a later stage of recurring crises. In the light of information gathered during the present study it is clear that the first crisis is not the direct result of emotional upset or mental trauma. The onset of an oculogyric crisis is almost certainly due to vestibular stimulation. The rather sudden and spontaneous tonic rotation of the eyes may well generate emotion and indeed fear, anxiety or grief, and the manifestations of emotional instability already described. The patient may try to devise a teleological explanation of the whole disturbance and thus comes to correlate the rolling of the eyes with some particular pattern of thought—likely enough to be associated in some cases with the feeling of guilt. As a result of a temporal relationship between the eye movements, the subjective experience on the one hand and some environmental factors (such as the presence of patient's relatives, meal times, etc.,) on the other hand, an association develops between them: in other words the pattern of a conditioned reflex is established. The environmental factors, however, are quite irrelevant to the *original* mechanism whereby the crises were generated. Recurring oculogyric crises in a particular environment condition the patient to these environmental factors or to certain thought processes and thus create a spurious concept of cause and effect. When conditioning has occurred these thought processes and "irrelevant" environmental factors may indeed assume major importance, for the patient may become the victim of suggestion based upon a complex conditioned reflex. Thus adventitious circumstances can eventually provide powerful sensory impulses precipitating motor upsets (oculogyric crises and all that goes with a crisis), notwithstanding the fact that the *first* crisis in the patient's experience was purely somatic in character.

The main thesis presented in this paper to account for the pathogenesis of oculogyric crisis is essentially somatic. That is to say the crises are the outcome of vestibular stimulation dependent on physical conditions. Nevertheless it must be considered that the clinical picture is complicated by the undoubted importance of psychological factors. Thus in the present series there is ample confirmation of the views of previous workers who stressed the significance of emotional disturbance which predispose to the onset of oculogyric crises. It is possible to visualize this sequence of events as a lowering of the threshold of the mechanism governing upward conjugate deviation of the eyes in oculogyric crisis. The lowered threshold may be due to neuronal activity in the diencephalon and upper brain-stem occasioned by the subjective aspect of emotion.

TABLE III.—TO SHOW DETAILS OF OCULAR LESIONS, DEGREE OF RIGIDITY AND EXCESS WAX IN THE EARS AND TYPE OF CRISIS IN THE 32 MEN WITH POSTENCEPHALITIC SYNDROMES

(Pupillary lesions were not included as the patients were on drug therapy for Parkinsonism)

No.	*Name*	*Age*	*Degree of rigidity*	*Eye lesion*	*Degree of wax r. ear*	*Degree of wax l. ear*	*Crises*
1	J. Bla	62	Moderate	None	2	2	None
2	J. Bel	62	Mild to moderate	None	2	1	None
3	J. McC	50	Moderate	Vertical nystagmus on movement	2	2	None
4	D. Gor	57	Moderate	Vertical and horizontal nystagmus on movement	1	2	Sweating crisis
5	A. Ead	46	Severe	None	2	2	None
6	J. McF	46	Severe	None	1	2	"screaming turns" (very infrequent)
7	N. San	47	Moderate	None	1	1	None
8	H. Dev	48	Severe	Nystagmus only during oculogyric crisis	1	2	Oculogyric crisis
9	T. Gal	48	Mild	None	0	0	None
10	J. Smi	53	Moderate	None	1	2	None
11	J. McI	58	Moderate	None	1	2	None
12	J. McM	50	Moderate	Dissociated eye movements. Diplopia	1	2	Sweating crisis
13	H. War	63	Moderate	None	1	2	None
14	J. Esp	50	Moderate	None	2	1	None
15	R. Pra	42	Moderate	Diplopia. Dissociated eye movements. ? slight weakness of right internal rectus. Nystagmus only during crisis	2	1	Oculogyric crisis mild sweating at times
16	M. Law	46	Severe	Horizontal and vertical nystagmus on movement. Some weakness of right internal rectus	2	1	Sweating crisis

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No.	*Name*	*Age*	*Degree of rigidity*	*Eye lesion*	*Degree of wax r. ear*	*Degree of wax l. ear*	*Crises*
17	R. Bro	51	Severe	None	2	1	None
18	J. Dea	56	Moderate	None	½	0	None
19	C. Han	50	Moderate	Some dissociated eye movements	2	1	None except for eye staring
20	P. Cam	42	Severe	Weakness both internal recti. Dissociated eye movement	2	2	None
21	J. Cam	57	Moderate	Diplopia third nerve palsy right side. Bilateral ptosis—more on right	1	2	Sweating crisis
22	P. Cad	45	Moderate	Horizontal and vertical nystagmus on movement. Diplopia	1	0	Mild oculogyric crisis
23	A. Hay	50	Moderate	Nystagmus on looking downwards	0 perforated eardrum	2	Mild oculogyric crisis
24	T. Pow	56	Moderate	Diplopia	1	2	Eye staring mainly but occasionally has true oculogyric crisis
25	J. McE	42	Mild	None	0	0	None
26	J. Nim	47	Moderate	Difficulty in moving the eyes without moving the head	0	1	Patient has hemi-ballismus He has periodic attacks of eye staring with head retraction
27	T. Wyp	54	Mild	None	1	1	None
28	C. Fea	55	Mild	None	1	0	None except for eye staring
29	D. Vil	48	Mild	None	0	0	None
30	W.S.	53	Moderate	None	½	2	Oculogyric and sweating crisis
31	T. Gar	37	Severe	Weakness of all movements. Cannot sustain eye movement except for forward gaze	0	0	None
32	F. Wal	47	Moderate	None	2	2	None

NOTE.—0=no wax at all. 1= moderate degree of excess wax. 2=complete blockage of the external auditory meatus.

TABLE IV.—DETAILS OF OCULAR LESIONS, THE DEGREE OF RIGIDITY, THE DEGREE OF EXCESS WAX IN THE EARS, AND THE TYPE OF CRISIS IN THE 35 WOMEN WITH POST-ENCEPHALITIC SYNDROMES

(Pupillary lesions are not included as the patients were on drug therapy for Parkinsonism)

No.	*Name*	*Age*	*Degree of rigidity*	*Eye lesion*	*Degree of wax r. ear*	*Degree of wax l. ear*	*Crises*
1	M. Dob	56	Severe	None	1½	2	None
2	K. Has	45	Severe	None	1½	2	None
3	C. Ros	71	Moderate	None	2	2	None
4	C. Jon	78	Moderate	None	2	2	None
5	A. McQ	44	Moderate	Vertical nystagmus	2	2	Oculogyric crisis. Vertigo sometimes during crisis
6	M. Cal	71	Moderate	None	0 Perforated eardrums	0	None
7	M. Fay	48	Mild	None	0	0 Perforated eardrum	None
8	A. Bis	53	Severe	Nystagmus in both directions on movement	½	1	Oculogyric crisis
9	A. Niv	41	Severe	Some weakness of left external rectus. Horizontal nystagmus on movement	1	0	"Screaming turns'
10	C. McK	57	Severe	Paralysis R. internal rectus. Vertical and horizontal nystagmus on movement	2	2	Oculogyric crisis. Vertigo sometimes present
11	J. Hug	50	Mild	None	0	0	None
12	R. Gra	52	Moderate	Nystagmus at rest. Diplopia	1½	2	Oculogyric crisis. Vertigo sometimes present. Diplopia worse during crisis
13	R. Cai	62	Severe	None	2	2	Oculogyric crisis
14	M. Fea	62	Severe	None	2	2	Breath holding attacks

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No.	*Name*	*Age*	*Degree of rigidity*	*Eye lesion*	*Degree of wax r. ear*	*Degree of wax l. ear*	*Crises*
15	M. Cra	40	Mild	Nystagmus during crisis only	1	1	Oculogyric crisis. Diplopia and mild vertigo during crisis
16	A. Sin	70	Moderate	None	1	1	None
17	M. McC	48	Mild	Cannot move R. eye to full range in both directions	0	½	None
18	C. Sco	74	Moderate	None	0	1	None
19	A. McL	54	Severe	Nystagmus during oculogyric crisis only	1½	2	Oculogyric crisis
20	A. Tan	51	Severe	None	1½	1½	None
21	A. Pol	54	Severe	? some weakness right lateral rectus. Nystagmus only during oculogyric crisis	2	2	Oculogyric crisis
22	E. McG	54	Moderate	None	2	1½	Sweating crisis
23	A. Mel	49	Mild	None	0	0	None
24	J. Pat	56	Moderate	Weakness R. external rectus. Nystagmus only during crisis	2	2	Oculogyric crisis. Vertigo sometimes present. Mild sweating crisis
25	C. McM	55	Mild to moderate	Weakness R. internal rectus. Diplopia. Nystagmus only during crisis	0	1	Oculogyric crisis. Diplopia worse during crisis. Vertigo sometimes present
26	M. Gil	49	Mild	None	0	2	Oculogyric crisis with marked photophobia. Vertigo sometimes present
27	M. Aus	58	Mild	None	0	0	None
28	R. Mon	39	Moderate	None	2	2	Sweating crisis
29	M. McL	56	Severe	Horizontal nystagmus on movement. Diplopia	1	2	Oculogyric crisis. No vertigo or diplopia during crisis

No.	*Name*	*Age*	*Degree of rigidity*	*Eye lesion*	*Degree of wax r. ear*	*Degree of wax l. ear*	*Crises*
30	A. Car	47	Severe	Weakness both internal recti. Dissociated eye movements. Diplopia	1½	2	None
31	H. McG	39	Moderate	None	0	½	None
32	E. McK	56	Moderate	None	2	½	None
33	A. McL	59	Mild to moderate	Diplopia occasionally	½	½	None
34	C. Bun	50	Mild	None	1	½	Oculogyric crisis. Vertigo sometimes during crisis
35	M. Rei	47	Mild	None	2	1½	Oculogyric crisis (infrequent). No vertigo or diplopia

NOTE.—0=no wax at all. 1=moderate degree of excess wax. 2=complete blockage of the external auditory meatus.

SUMMARY

A study of 67 patients with post-encephalitic Parkinsonism revealed three types of crisis: they can be described as oculogyric, sweating and breath-holding.

The clinical accompaniments of oculogyric and sweating crises are described. Attention is drawn to the vasomotor changes which occur during severe oculogyric crises.

The pathogenesis of the oculogyric is discussed. It is suggested that ocular deviation is the consequence of a vestibulo-ocular reflex in patients with brain-stem lesions involving the vestibular pathway. The emotional changes which accompany oculogyric crises are probably the result of stimulation of the diencephalon.

The role of emotion in precipitating oculogyric crises is confirmed. When emotion is known to play a part, it is suggested that the mechanism includes a conditioned reflex. Alternatively it may be that the onset of emotional disturbances sometimes permits activity in the vestibulo-ocular reflex; activity which in the non-emotional state is materially inhibited.

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LEGENDS FOR PLATE XLVI

FIG. 1A.—Severe oculogyric crisis in woman aged 56: flushed face, suffused conjunctivæ, and frothing at mouth. B.P. rose to 204/110: heart-rate 96.

FIG. 1B.—Same patient as 1A when not in crisis. B.P. 160/90: heart-rate 72.

FIG. 2A.—Mild oculogyric crisis in man aged 42. Flushed face, but no significant rise in B.P. or in heart-rate.

FIG. 2B.—Same patient, when not in crisis.

FIG. 3.—Patient voluntarily looking upwards. Note absence of wrinkling of forehead.

PLATE XLVI

FIG. 1A.

FIG. 1B.

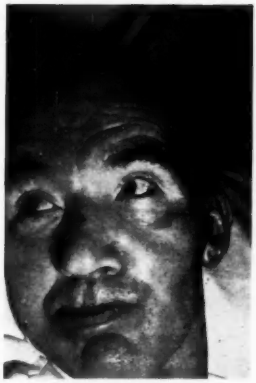

FIG. 2A.

FIG. 2B.

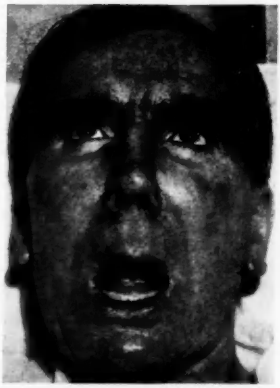

FIG. 3.

To illustrate article by Gilbert Onuaguluchi.

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POSITIONAL NYSTAGMUS OF THE CENTRAL TYPE AS EVIDENCE OF SUBTENTORIAL METASTASES

BY

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INTRODUCTION

THE general neurological features of metastases in the central nervous system have been the subject of a number of reports (Globus and Selinsky, 1927; Fried and Buckley, 1930; King and Ford, 1942; Lesse and Netsky, 1954, and Weinberg, 1954). There has, however, been no mention of the neuro-otological aspects of metastases in the central nervous system, although Störtebecker (1954) noted that vertigo was a first or early symptom in 24 per cent of metastatic brain tumours. In Nylén's (1939) large series of cases of verified brain tumours that received a neuro-otological examination, there were a few metastatic tumours, but the specific neuro-otologic findings in these cases are not mentioned, despite the frequency with which vertigo was noted in this series.

During the course of neuro-otological examinations in the past few years we have noticed the association of a specific neuro-otological sign, namely positional nystagmus of the central type, with cases of subtentorial metastases. This sign can, of course, also be present in other subtentorial tumours, but in our experience it is rarely seen in supratentorial tumours. However, what has impressed us particularly has been the appearance at a neuro-otological clinic of patients complaining of vertigo and presenting with positional nystagmus of the central type, the primary cause for which in 4 out of 6 cases to be reported turned out to be an unsuspected carcinoma of the bronchus. As early as 1911, Heinemann pointed out that primary carcinomas could pursue a latent course, the only symptoms being those of metastases in the central nervous system. This applies especially to carcinoma of bronchus, where neurological symptoms are the first clinical evidence of the neoplasm in a half of those cases with cerebral metastases (Conforti, 1956).

A description of 6 cases in this paper will illustrate the significance of a finding of positional nystagmus of the central type and its value as a clue in the diagnosis of growths outside the skull.

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Definitions

Our use of the term positional nystagmus is in the more restricted connotation of the British school (Dix and Hallpike, 1952; Cawthorne, 1954), where stress is laid on the pattern of the nystagmus. In the paroxysmal type, the nystagmus appears a few moments after adopting the critical position (usually with the head back and to one side), lasts for anything up to ten seconds and then dies away. It does not reappear even if the critical position is resumed until several minutes have elapsed. It is accompanied by vertigo which is often severe. This paroxysmal type may be due to a lesion in the utricular part of the vestibular labyrinth.

In the so-called central type, the nystagmus appears as soon as the critical head position is assumed and it continues so long as that position is maintained and it reappears as soon as the position is resumed. The accompanying vertigo is rarely severe. It has to be distinguished from an accentuation of an already existing nystagmus which may be temporarily increased by a change in head position.

Case Histories

Case 1.—E. G. W., male, aged 48.

This postman was seen at the neuro-otological clinic on September 23, 1959. He complained of recurrent attacks of giddiness for the past six months, and had had two "blackouts" in the past eight months.

On the day of the first "black-out" eight months previously, he was seen at a hospital casualty department where a clinical examination showed no abnormality. An X-ray of the skull and an EEG were also normal. Six weeks later, a second clinical examination in a neurological clinic again showed no abnormality but a second EEG showed a few episodes of low voltage 2–6 c/s activity in the lower left frontal areas. A diagnosis epilepsy of late onset was made. Six months later, nystagmus was observed and the influence of posture on the nystagmus noted. The neurologist considered that vestibular neuronitis might be present in addition to epilepsy and the patient was admitted to hospital for investigation and referred for a neuro-otological opinion.

Neuro-otological examination showed no visible abnormality in the ear, nose or throat. A pure tone audiogram was normal. The patient had an unsteady gait with a wide base and fell to the right when standing with the eyes closed. There was a first degree spontaneous nystagmus to the left with some unsustained spontaneous nystagmus to the right and above. Both optomotor and caloric-induced nystagmus showed a directional preponderance to the left. The positional test showed a nystagmus of central type in the right head down position. A diagnosis of a posterior fossa lesion, possibly due to a metastatic carcinoma, was made.

Neurological examination showed a slight tendency to past-pointing with both upper limbs, but more so on the left. There was no papillœdema.

An X-ray of the chest showed a large mass with a well-defined rounded edge extending anterolaterally from the left hilum. There was also some obstructive emphysema at the left base. An E.S.R. was 11 mm. in the first hour. Another EEG showed, in addition to the slow wave disturbances occurring on the left side, a widespread rather slow alpha rhythm and scattered theta waves.

Comment.—This case history indicates a primary carcinoma bronchus on the left side with secondary deposits, first, in the lower left frontal area, and then in the cerebellum.

Bailey (1948) had said that any patient in middle-age or older who develops focal cerebral symptoms, not obviously luetic or vascular in origin, should have the chest X-rayed. Acceptance of this dictum would have given the correct diagnosis six months earlier. The brain may be the sole site of remote metastasis especially in the case of carcinoma bronchus (Rupp, 1948) and the primary and the secondary neoplasm may be successfully removed (Ballantine and Byron, 1948). However, judging by the train of symptoms in this case, the interval between the two intracranial deposits was a matter of a few weeks only. The possibility of successful surgical intervention in this case was therefore remote.

Case 2.—F. W., male, aged 62.

This chartered accountant was seen at the neuro-otological clinic on November 9, 1955. He complained of unsteadiness for the past ten days. There had been periodic nausea for four days and he had vomited once three days before, but there had been no deafness or tinnitus. A "muzziness' of the head was noticed, but no headache.

Seven years previously, he had been troubled with malaise and weak legs, of insidious onset. This difficulty had progressed for one month, at the end of which time he could only shuffle along. The condition then improved and at the end of another month he felt well again. An X-ray of the chest at that time was reported to show evidence of bronchiectasis. Periodically since then, he has had burning pains in both legs.

Neuro-otological examination showed no visible abnormality in the ears, nose or throat and a pure tone audiogram was normal. The patient had an unsteady gait with a suggestion of a broad base. With the eyes open, his stance was steady, but with the eyes closed he tended to fall to the right. There was no spontaneous nystagmus and the optomotor nystagmus was normal, but there was a slight directional preponderance to the left of the caloric-induced nystagmus. A central type positional nystagmus was observed with the head back in the sagittal plane and to the right hand side. A diagnosis of posterior fossa lesion possibly a secondary neoplasm was made.

Neurological examination showed an intention tremor of the right hand and the heel-knee test was unsteady on both sides, but more so on the left. There was no papillœdema. A neurological opinion was that the patient had cerebellar ataxia due to a brain-stem lesion, possibly demyelinating.

X-rays of the chest and skull showed no abnormality. Routine examination of the blood gave normal results including a negative Wassermann reaction and an E.S.R. of 4 mm. in the first hour. The cerebrospinal fluid contained 180 mg. protein per 100 ml. and there was one lymphocyte per c.mm. A normal Lange curve was obtained.

Ventriculography indicated a left cerebellar hemisphere tumour.

Operation on November 17, 1955: Posterior craniotomy disclosed a left cerebellar secondary carcinoma which was excised.

Histological examination of the tumour showed a rapidly growing secondary carcinoma with a papillary pattern. No definite origin could be ascertained; it could have been a bronchial carcinoma.

The patient had a satisfactory post-operative recovery. A search for the primary neoplasm, including contrast radiography of the alimentary and urinary tracts and measurement of the serum acid phosphatase, was unrewarding.

The patient was well for about a month after leaving hospital, at the end of which time he developed attacks of paræsthesiæ in the right hand and, on one occasion, twitching of the right face. Neurological examination then showed a marked weakness of the right hand and definite astereognosis, although the cerebellar symptoms and signs had completely resolved. An EEG confirmed the clinical localization in the centre of the left hemisphere. Moreover, X-ray of the chest now showed a parenchymal opacity

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in the left upper zone with some doubtful enlargement of the left hilum and a faint opacity in the first left interspace.

Comment.—This is similar to the first case in having secondary deposits in the cerebellum and the left cerebral hemisphere from a primary carcinoma of the bronchus. In this case, however, the metastasis in the cerebellum appeared first and there was an interval of two or three months before the other intracranial metastasis appeared. Successful surgical intervention might therefore have been a theoretical possibility. In contrast to the first case, the primary lesion was not detectable until two or three months after the onset of symptoms referable to a metastasis. This is not uncommon. Russell and Rubinstein (1959) mention a 54-year-old male whose carcinoma bronchus was not diagnosed until four years after a secondary carcinoma had been resected from the left occipital lobe. At the time of operation, an X-ray of his chest was normal.

The episode of weakness of the legs that antedated the present illness by seven years is of interest. The history was very suggestive of a peripheral neuropathy. Burning pains in the legs are also characteristic of the carcinomatous neuropathies. Arrest or remission of a carcinomatous neuropathy has been a common finding (Lennox and Pritchard, 1950; Henson *et al.*, 1954). Characteristically, too, a carcinomatous neuropathy may precede the appearance of the neoplasm. However, the longest intervening period that has been reported with this sequence was a patient with a sensory neuropathy whose bronchial carcinoma could not be found until three and a half years after the onset of neurological symptoms (Ironside, 1953). Heathfield and Williams (1954) stress the necessity for a thorough chest investigation in all cases of peripheral neuropathy or myopathy in the older age groups. In their opinion, the neuropathy is so characteristic of the syndrome that, even if chest X-rays show nothing abnormal, bronchoscopy should be performed.

Case 3.—M. F., female, aged 20.

This clerk was seen in the neuro-otological clinic on August 14, 1957. She complained of dizziness over the past month. Attacks of dizziness were brought on by head movements.

For the past eight months, she had had headaches which were periodic to begin with but were now almost continuous and very severe. The headaches commenced in the left temporal region and radiated to the occipital region, especially the left side. Over the period in which she had been subject to headaches, there had been periodical visual disturbances: coloured zigzags appeared in the right lower visual field. There had also been repeated vomiting in the past three weeks, sometimes as many as five times each day. During this same period, she had also had attacks of feelings of numbness in the right foot, radiating to the thigh.

The family history included migraine (father and mother) and epilepsy (a brother).

Three months ago, she was seen at an ophthalmic hospital. Migraine was diagnosed and her spectacles altered. Two months later she was subject to further investigations in hospital and discharged on phenobarbitone and iron medication.

The patient's past surgical history disclosed that she had had a dysgerminoma removed from the right ovary just over eighteen months ago. The operation had been preceded by periodic pains in the right iliac fossa for four years.

Neuro-otologic examination showed that there was no visible abnormality in the ears, nose and throat. The pure tone audiogram was normal. Gait, stance and optomotor nystagmus were normal and there was no spontaneous nystagmus. The caloric-induced nystagmus was prolonged and there was a vertical central type positional nystagmus directed towards the chin in all three head positions. This positional nystagmus was most noticeable in the right head down position, where it caused some distress.

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Neurological examination showed that the outstretched right arm fell away a little and there was generalized hypotonicity of the limbs. There was no papilloedema.

X-rays of the skull and the chest were normal. The E.S.R. was 11 mm. in the first hour. The Wassermann reaction on the blood was negative. The EEG showed runs of 5 c/s to 6 c/s activity on the left side and, also on the left side, a prominent sharp-wave abnormality which reversed phase mid-temporally and persisted on overbreathing. The cerebrospinal fluid was clear and colourless, but contained 170 mg. protein per 100 ml. and 101 lymphocytes per c.mm.

An A.E.G. indicated a posterior fossa lesion impinging on the ventricular system. The aqueduct was kinked a little, 5 mm. beyond the posterior commissure and possibly displaced forwards. The upper border of the fourth ventricle was rounded more than usual and possibly displaced downwards and forwards. There was also marked dilatation of the temporal horns out of all proportion to the concomitant dilatation of the lateral ventricles, which appearances were therefore those of cerebral atrophy.

Operation: subtentorial decompression on August 16, 1957, showed that the dura was under tension and the cerebellar tonsils were down at the level of C2, the left being lower than the right. No tumour, however, was seen. A post-operative course of deep X-ray to the cerebellum followed.

Follow up: when the patient was seen three months later, she was extraordinarily well with practically no physical signs. Unfortunately, in the following year she rapidly deteriorated and became unable to walk or to see to read.

Comment.—Dysgerminomas, comprising about 3 per cent of all primary malignant ovarian tumours (Klaften, 1934,) are uncommon. Less than 500 cases have been reported to date. Hæmatogenous dissemination is rare (Föderl, 1938; Sjövall, 1943; Santesson, 1947) and metastases to the brain from this type of ovarian neoplasm do not appear to have been previously described. This case also represents an exception to Christensen's (1949) rule that the origin of metastatic brain tumour is generally above the diaphragm. The interval of about a year between the removal of the primary growth and the onset of symptoms due to brain metastases is not remarkable. Gutmann (1940) reported a case in which metastases to the brain occurred eighteen years after operation for an ovarian malignancy.

This patient also showed a raised E.S.R. (upper limit of normal in women by the National Hospital's method is 6 mm. in the first hour) and both Sjövall (1943) and Rieben (1948) have stated that a metastasizing dysgerminoma is accompanied by a raised E.S.R. Rieben (1948) stresses the importance of measuring the E.S.R. in following-up cases of dysgerminoma.

The patient's response to radiotherapy is in accordance with the consensus of opinion that dysgerminomas and their metastases are very radiosensitive (Knottmeier, 1952).

Case 4.—J. C., male, aged 67.

This business man was visited at his home on February 9, 1959. He complained of dizziness, blurring of vision and nausea, all of which had been increasing during the previous few weeks. There had been no headaches.

Eight months previously, he had developed some glands on the right side of the neck. One of these had been removed and found to be an adenocarcinoma. Full investigation at that time, including bronchoscopy, œsophagoscopy and contrast radiography of the upper digestive tract, failed to disclose a primary lesion. About three months later, he developed a feeling of general weakness, especially of the legs, together with nausea in the mornings.

A second clinical examination two months ago indicated diminished aeration of the left upper lobe and dragging of the trachea over to the left side. There were no abnormal neurological signs. Screening and a P.A. chest film at the time of the examination was reported to show an elongated, fairly sharply defined opacity above the

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aortic arch adjacent to the left side of the trachea. Digital examination indicated this to be a separate mass from an adenoma in the left lobe of the thyroid which was placed higher up and moved upwards on swallowing, whereas the observed opacity in the anterior mediastinum was fixed. In addition, the X-ray was reported to show a multiple cystic condition of the right upper and middle zones, a change that had been noticed on a routine chest X-ray nearly two years previously. Consequently, a diagnosis of primary carcinoma of one of the smaller bronchi in the left upper lobe segment was made. However, this patient was also examined by a number of other physicians at that time and the consensus of opinion was that there was no evidence of a carcinoma of the bronchus.

Neuro-otological examination showed no visible abnormality of the ears, nose or throat. There was a spontaneous horizontal nystagmus with gaze to the right and some irregular movement of the eyes with the gaze to the left. The positional test showed that this nystagmus was very much increased in both the right and the left head down positions, especially the latter position. This positional nystagmus was not fatiguable. A posterior cranial fossa lesion probably due to a secondary deposit was diagnosed.

Neurological examination ten days later was said to indicate a small secondary deposit in the region of the fastigial nuclei of the cerebellum. There was no papillœdema.

X-rays of the skull and petrous bones were normal, but further X-rays of the chest left no doubt about the presence of a mass in the superior mediastinum to the left of the trachea. Tomography indicated that the opacity consisted of intra- and extrapulmonary portions and it was considered that the most probable diagnosis was a primary peripheral bronchial carcinoma in the medial portion of the apical segment of the left upper lobe, associated with a glandular mass in the left side of the superior mediastinum.

Meanwhile, further examination of the cervical lymph node that had been removed earlier showed that the better differentiated columnar epithelium in parts of the tumour appeared to be equipped with rudimentary cilia. An opinion was therefore given that the most likely primary site was in the bronchus.

The E.S.R. was 28 mm. in the first hour.

In the first half of April 1959 a course of radiotherapy was given to the posterior cranial fossa without success. The patient then showed meningism, sensory loss in the area of the left ear, diplopia, a left lower motor neuron facial palsy and partial left deafness. There was still no papillœdema and no enlargement of the liver.

The patient gradually deteriorated and died about two months later.

There was no necropsy.

Comment.—Here we have a carcinoma of the bronchus which first presented as a cervical lymphadenopathy, and there were no chest signs until six months later and even then the signs were equivocal. Dizziness developed and a central type positional nystagmus was observed before a diagnosis of bronchial carcinoma could be made unreservedly. The weakness of the lower limbs which developed shortly after the biopsy of the lymph node may suggest a subclinical carcinomatous peripheral neuropathy. Subsequent meningism and involvement of the left fifth, sixth, seventh and eighth cranial nerves indicated secondary deposits in the meninges or extension of the cerebellar metastasis to the meninges.

Case 5.—E. R. B., male, aged 59.

This company director was seen on March 22, 1957. He complained of feeling unsteady on his feet for several weeks.

The patient was well until five weeks previously when his gait became unsteady and progressively deteriorated. There was no unsteadiness when he was sitting or lying

down and there were no other symptoms referable to the ears, nose or throat or to the auditory or vestibular systems. However, during the past fortnight, he had had right parietal headaches and had had double vision. The headaches lasted for a few minutes only and occurred in the mornings. The diplopia occurred on looking up, one object being above the other.

Neuro-otological examination showed no visible abnormality of the ears, nose or throat and the hearing was normal. He had a moderately ataxic gait with a wide base. There was no spontaneous nystagmus, but the positional test showed a central type positional nystagmus with the head back and to the left. Both the optomotor and the caloric-induced nystagmus were normal. A metastatic carcinoma involving the vestibular nuclei in the cerebellum was considered to be the most likely lesion.

Neurological examination showed slight weakness of elevation of the left eye and the right pupil did not react quite as well as the left. There was no papillœdema, but there was moderate ataxia of both lower limbs. A cerebellar lesion, probably due to secondary deposit, was diagnosed. However, a second neurological examination two weeks later showed a left extensor plantar response, astereognosis with respect to the left hand and a reduction of the nasal half of the right visual field. A space occupying lesion of the right hemisphere was diagnosed.

An X-ray of the skull showed that the posterior clinoid processes and the floor of the pituitary fossa were somewhat more decalcified than usual for the patient's age. This change was considered to be due to vascular changes associated with tortuous vessels rather than an erosion due to raised intracranial pressure. The chest X-ray was normal.

The E.S.R. was 8 mm. in the first hour.

Lumbar puncture showed the cerebrospinal fluid to be at a pressure of 255 mm. It contained 14 lymphocytes per c.mm. and 340 mg. protein/100 ml.

The EEG showed a focal abnormality in the posterior part of the right parieto-occipital region. These changes were considered to be compatible with a tumour.

Ventriculography on March 17 showed marked depression of the roof of the right lateral ventricle in its middle and trigonal portions. The appearances were those of a large right-sided parasagittal space occupying lesion in the parietal region.

Operation on April 17, 1957: right parietal craniotomy disclosed a soft broadened convolution in the posterior part of the wound near the mid-line. After needling showed a small cystic cavity in this region, a typical secondary carcinoma at a depth of 1 cm. was removed without difficulty.

After some initial post-operative recovery, the patient gradually became drowsy a fortnight later. Confusion and disorientation developed and he died two months after the operation after four days in coma.

Necropsy was not performed.

Comment.—Here again we have a case of primary extracranial malignancy presenting as an intracranial lesion. The course of the disease suggests that there was a secondary deposit first in the cerebellum to the left of the mid-line, and then in the cerebrum in the right hemisphere. The site of the primary lesion was never discovered but was probably in one of the bronchi.

Case 6.—C. S. R., female, aged 61.

This woman was seen on February 10, 1960. She complained of general unsteadiness of three weeks' duration. The unsteadiness was accentuated when she lay back in bed, especially when she turned to the right. She also had some difficulty in chewing on the right side.

The previous medical history included removal of the right breast three years previously for a spheroidal-cell carcinoma. The operation was followed by deep X-ray therapy. Two and a half years later, lymph nodes were removed from the right

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posterior triangle of the neck because of metastatic involvement. A further course of deep X-ray therapy was also given to the patient.

Examination of the ears, nose and throat showed no visible abnormality. Neuro-otological examination showed a positional nystagmus of the central type when the head was put back and to the right. The only abnormal finding on general neurological examination was a paralysis of the motor part of the right trigeminal nerve.

X-rays of the skull showed evidence of secondary deposits in the parietal region of the skull and in the region of the right foramen ovale.

A diagnosis was made of mammary carcinoma metastases in the base of the skull and in the posterior cranial fossa, with involvement of the vestibular nuclei in the cerebellum.

The patient rapidly deteriorated and died six weeks later.

Comment.—The unusual feature here is the involvement of the motor part of the trigeminal nerve by a metastasis. The case demonstrates a characteristic feature of patients with the central type of positional nystagmus. This is the rapidly fatal outcome that invariably ensues.

Discussion

Under this heading, it will be profitable to discuss the relative specificity of the sign, i.e. central type positional nystagmus, in the diagnosis of subtentorial metastases. It is convenient to do this from anatomical and pathological view points.

Our central type positional nystagmus is considered to be indicative of a lesion of the vestibular centres of the cerebellum. It may, however, be present without any other cerebellar signs. Nylén (1939) has said that positional nystagmus may be the only neurological sign of a brain tumour. There seems no reason to doubt that this statement does not apply equally well to secondary as well as primary neoplasms.

Is there any predilection for secondary malignancies to involve the cerebellum? Of cases with single brain metastases, the cerebrum is involved three times as frequently as the cerebellum (Ask-Upmark, 1956). This applies equally well whether the primary is a carcinoma of bronchus (Meyer and Reah, 1953) or otherwise (Lenshoek, 1956), although Feyzoulayev (1958) has stated that intracranial metastases from carcinoma of breast are preferentially localized in the cerebellum and brain-stem. However, the ratio of the weight of the cerebrum to that of the cerebellum is 9:1 (Rexed, 1956). One must therefore conclude that the frequency of subtentorial metastases is at least three times greater than one would expect if the distribution were dependent mainly on the bulk of the involved structures. Ask-Upmark (1956) has attributed this to the cerebellar tissues being a more fertile soil for localization of secondary deposits. It is noteworthy that the carcinomatous degenerations also show a predilection for the cerebellum rather than the cerebrum (Brain *et al.*, 1951).

What is the probability of a central type positional nystagmus being due to a mestastasis? All the patients in this series had a secondary deposit in the cerebellum, but this represents but a small proportion of the patients

seen with positional nystagmus of the central type. Other tumours in the posterior fossa and degenerative conditions within the cerebellar can also be responsible. The apparent equivalent prevalence of metastases and primary neoplasms involving the vestibular centres in the cerebellum is in contrast to the much smaller proportion of metastatic tumours amongst brain tumours as a whole. It is perhaps attributable to an extension of the hypothesis of the "cerebellar-selectivity" of metastases to the nervous system which Ask-Upmark has previously remarked upon. One might therefore hypothesize a predilection of metastases for tissues in and around the vestibular centres in the cerebellum.

Since tumours form a common cause of central type positional nystagmus, observation of this sign invokes the question "Is it primary or secondary?" In a recent paper on brain metastases, Barbizet and Labet (1956) say that, from the age of 40 years, every tumour ought to be suspected of being metastatic. Our case of the 20-year-old girl implies that we must lower this age limit. In recent studies of metastatic tumours of the brain, both Störtebecker (1954) and Ask-Upmark (1956) conclude that the symptoms of metastatic brain tumours do not differ essentially from those of primary brain tumours, although Globus and Selinsky (1927), King and Ford (1942), Balek and Smetanay (1955) and Feyzoulayev (1958) have pointed to the frequent acute or subacute onset which simulates a vascular lesion. Boeri and Negri (1957) have also stressed the acute/subacute initial phase together with an irregular progression associated with partial regressions. Bailey (1948) has mentioned the intensity of the headache and the mental confusion, which are out of all proportion to the intracranial tension, whilst Lesse and Netsky (1954) mention that patients with intracranial metastases are not likely to develop extrapyramidal symptoms. In the sphere of special investigations, Castorina and Severini (1955) claim that there are angiographic features that differentiate between metastatic and primary brain tumours, but Gloning (1955) asserts that there are no uniform angiographic patterns in brain metastases except for the case of hypernephroma deposits. However, all these points which may help in the differential diagnosis of primary and secondary tumour are mainly with respect to supratentorial lesions. The diagnosis of a secondary, as distinct from a primary, subtentorial tumour is more difficult. Headache, for example, was prominent in only two of the six cases of subtentorial metastases which we have described here.

This probability that a central type positional nystagmus is due to a neoplasm, taken together with the inability to differentiate between primary growths and metastases, means that we should search for a possible primary neoplasm in all cases of central positional nystagmus. The pattern of such a search will be governed by the probability of subtentorial metastases arising from primary malignancies in given organs. This

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probability pattern will itself be determined by

(*a*) the relative prevalence of primary malignancy in various organs;

(*b*) the degree to which these malignancies metastasize; and

(*c*) the affinity of these metastases for the cerebellum.

Factors (*b*) and (*c*) can be lumped together as a single factor, i.e. the frequency of metastasis to the cerebellum. As yet, no data are available for the cerebellum alone. We may therefore assume that the relative frequencies of metastasizing to the cerebellum are the same as to the brain as a whole. Considering Feyzoulayev's (1958) paper with reference to the proclivity of breast carcinoma metastases for the cerebellum and brainstem, this assumption may not be entirely correct. It does, however, serve as a base-line in the absence of more definite data. The brain is eventually affected in a very high proportion of cases of chorionepithelioma (Russell and Rubinstein, 1959), in 68 per cent of all sarcomas (Rau, 1921), in 50 per cent (Bailey, 1948) to 76 per cent (Walther, 1948) of malignant melanomas, in 30 per cent of carcinoma bronchi (Bailey, 1948; Galluzzi and Payne, 1956), in 8 per cent (Hannemann, 1937) to 16 per cent (Brunner, 1936) of hypernephromas and in 5 per cent (Bailey, 1948; Gutting, 1940) to 15 per cent (Lenz and Freid, 1931) of mammary carcinoma. However, owing to the high prevalence of carcinoma of bronchus in the male and of carcinoma of breast in the female, these two primary types assume relatively greater importance as causes of cerebellar metastases. A geographical factor also seems to be involved since the most common site of the primary for a brain metastasis differs between various countries. In Meyer and Reah's (1953) London series, the bronchus was the commonest site (54 per cent of cases) of the primary, whilst no other individual site accounted for more than 9 per cent of cases. These authors did, however, indicate that the proportion of carcinoma of breast bronchus cases was inflated, and that of carcinoma of breast cases, deflated, owing to selective factors. Störtebecker's (1954) Stockholm series showed that hypernephroma was the most common (20 per cent of cases) primary neoplasm, and non-renal sites did not, individually, account for more than 15 per cent of cases. Riser *et al.* (1956) Paris series showed that the primary growth was in the breast in 42 per cent of cases and in the lung in 26 per cent of cases.

The discovery of an extracranial primary growth poses two further questions:

(i) Is the brain deposit single or multiple? and

(ii) Are there associated metastases, i.e. deposits elsewhere in the body.

The probability is greater than 0·5 that there are multiple and associated metastases (Galluzzi and Payne, 1956).

The answer to the first question is given by the results of a neurological examination, together with the help of EEG findings. In this respect, however, it is to be noted that the EEG is unreliable in detecting subten-

torial metastases (Smith, 1957). Störtebecker (1954) says that an E.S.R. of greater than 50 mm. in the first hour indicates multiple brain metastases.

The second question is answered by examining the probable sites of multiple metastases. For primary carcinoma bronchus with brain involvement, Galluzzi, and Payne (1956) give the relative probabilities of involvement of other organs as pancreas > kidneys > adrenals > thyroid > spleen > liver, with final involvement of the pancreas in about half the cases and of the liver in nearly a quarter.

Although central type positional nystagmus may be the only neurological sign of a brain tumour (Nylén, 1939), it does not exist without the symptom of vestibular dysfunction, i.e. vertigo (Cawthorne, 1954). It is to be stressed, however, that our definition of vertigo is an hallucination of movement. This definition therefore embraces both oscillopsia (Brickner, 1936) and sensations of unsteadiness, in addition to the usually accepted more generalized oculogyric and oculogravic illusions. An analysis of the vestibular symptoms associated with central type positional nystagmus indicates that unsteadiness, movement-dependent oculogyric illusions and oscillopsia are about equally prevalent. The presence or absence of vertiginous symptoms is therefore important and, as Meyer zum Gottesberge (1948) remarks, the positional test is indispensable in the diagnosis of vestibular dysfunction.

It is interesting to note that none of these cases had papillœdema. Papillœdema was infrequent (23 per cent of cases) in King and Ford's (1942) series of brain metastases from carcinoma of lung, although Störtebecker (1954) found papillœdema in 82 per cent of his series of metastatic brain tumours. It is not really permissible, however, to compare these figures since both King and Ford's and Störtebecker's series apply to metastases to the brain as a whole, and the primary growth was carcinoma of bronchus in only 16 per cent of Störtebecker's series.

Summary

Six cases are reported which illustrate successively the importance of (*a*) the positional test in the investigation of vestibular symptoms, (*b*) the importance of subtentorial metastases as a cause of central type positional nystagmus, and (*c*) the presentation of extracranial primary tumours with this specific neuro-otological sign.

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MEGALENCEPHALY, INTERNAL HYDROCEPHALUS AND OTHER NEUROLOGICAL ASPECTS OF ACHONDROPLASIA

BY

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INTRODUCTION

MAJOR neurological features of achondroplasia which have been previously recognized centre about the enlargement of the head and compression of the spinal cord. Both of these contribute to a high neonatal mortality rate (Cohn and Weinberg, 1956; Draps, 1952; Mørch, 1941; Porak, 1890; Potter, 1952; Potter and Coverstone, 1948), and have been attributed to premature synostoses of the pedicles of the vertebræ (Vogl and Osborne, 1949) and of the base of the skull (Collmann, 1901; Jansen, 1912; Meyer, 1924), producing obstruction of the ventricular fluid circulation with internal hydrocephalus (Cohn and Weinberg, 1956; Dandy, 1921; Draps, 1952; Jansen, 1912; Luck, 1950; Russell, 1949; Spillane, 1952; Welter, 1936) or compression of the medulla and spinal cord with paraplegia (Jansen, 1912; Spillane, 1952; Vogl and Osborne, 1949) or death (Collmann, 1901; Jansen, 1912; Luck, 1950; Potter, 1952). Those investigators who have found no hydrocephalus (Broggi, 1933; Gruber, 1936; Jenkinson and Kinzer, 1941; Mørch, 1941; Potter, 1952; Russell, 1949; Spillane, 1952) have attributed the enlargement of the head to other

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bony abnormalities of the cranial vault (Dietrich-Weinnoldt, 1926; Gruber, 1936; Welter, 1936) or have offered no other explanation for it.

Recent examination of 5 cases at autopsy has revealed that the enlargement of the head was due to enlargement of the brain, a true megalencephaly, rather than to dilatation of the ventricles. Although Wilson (1934) and Jacob (1956) have extensively reviewed the subject, relatively little is yet known about the pathogenesis of megalencephaly, The presently reported incidence of megalencephaly in achondroplasia contributes little to this problem but suggests that achondroplasia may not be considered merely a defect in bone growth.

Case Reports

Case 1.—This 1,785 grammes white male infant was born at the Jefferson Davis Hospital to a 21-year-old woman after an estimated 30 to 32 weeks' gestation. The only complication of pregnancy was pre-eclampsia, which was controlled with mercuhydrin and Diamox. There was no family history of achondroplasia. No other illnesses were known in the father, mother, or their families. Labour was induced by rupturing the membranes, and an uncomplicated low forceps delivery was carried out.

Physical findings.—The general appearance of the infant was quite abnormal; the thorax was small and constricted, the abdomen large and protuberant. Particularly notable were the short extremities, broad hands and feet, and short digits. The head was large; the fontanelles were widely open, and the cranial sutures separated. The crown-heel length was 37 cm., chest circumference 23 cm., and head circumference 33 cm. The infant exhibited immediate respiratory difficulty, as demonstrated by poor aeration of both lungs and suprasternal retraction, and his immediate condition following birth was considered poor.

Laboratory data.—The infant's blood group was Rh negative, as was the mother's. The indirect Coomb's test was negative. Serologic examinations of the blood of the infant and of the mother were negative for syphilis. Chest X-ray of the infant disclosed little evidence of aeration in either lung.

Course.—Following delivery respiratory difficulty continued, and the liver was felt 4 to 5 cm. below the right costal margin. He was digitalized and given achromycin, but failed to show any improvement. Death occurred fourteen hours after birth.

Autopsy (A–57–310; D–504) was performed by Dr. S. Singleton and revealed the body weight to be 1·86 kg. Body measurements from head to rump and head to foot were 20 cm. and 36 cm., respectively. The distance between the bottom of the inguinal ligament and the bottom of the foot was 7 cm., the shoulder to wrist length 6·5 cm., and the neck to scrotum distance 18 cm. The anterior fontanelle measured 3·5 by 6·0 cm. There was marked prominence of the parietal bones, and the cranial sutures were widely separated.

The fresh brain weighed 400 grammes, and after fixation in 10 per cent formalin the weight was 555 grammes. There was a marked discrepancy in the sizes of the cerebral and the cerebellar hemispheres, the cerebellum being relatively small and the fore-brain being relatively large. Marked congestion of the cerebral veins was present with small areas of subarachnoid hæmorrhage over the lateral and posterior aspects of the cerebral hemispheres.

Coronal sections through the cerebral hemispheres revealed only slight symmetrical enlargement of the ventricles (fig. 1, Plate XLVII). The choroid plexuses were congested. A small cavum septi pellucidi was present.

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Final pathologic diagnoses included achondroplasia; prematurity; immature kidney, heart and liver; parenchymal hæmorrhage of the lungs (segmental); and aspiration of meconium and vernix.

Case 2.—This 5½ months old white male was first admitted to the Methodist Hospital in February 1958 for investigation of what appeared to be an abnormal rate of increase in head size. He had been delivered by Cæsarean section because prepartum X-rays had revealed a head size compatible with hydrocephalus and a cephalopelvic disproportion. At birth the head circumference was 39 cm., and he was diagnosed as achondroplastic, not hydrocephalic.

His development had been normal as far as could be ascertained. He had been noted to follow light almost since birth. He had smiled and reached for objects since the age of 3½ months. At about 3 to 3½ months he began turning over in bed and creeping about in his crib, but he had not been seen to sit up by himself.

Past and family history.—There had been no known prior illnesses. He had not been a feeding problem, nor had there been any vomiting or irritability. Two siblings, aged 4 and 2 years, were normal. No history of other cases of achondroplasia in the family could be elicited.

Physical findings.—The head circumference at 5½ months was 49 cm., chest 36 cm., and length 61 cm. The anterior fontanelle was concave, and the cranial sutures were not separated. There appeared to be a slight prominence of the frontal bones. The abdomen was protuberant. His fingers and hands were short and broad. An abnormal degree of mobility was noted to be presented at the knee and hip joints bilaterally. The neurological examination was within normal limits.

Laboratory data.—Urinalysis and complete blood count were normal except for 10 per cent eosinophiles in the blood. X-rays of the ribs, hands, feet, and long bones showed changes associated with achondroplasia. Skull X-rays revealed a relatively large calvarium with disproportion between the size of the skull and the facial bones, probably associated with achondroplasia, but equivocal flattening of the tuberculum and of the dorsum sellæ raised the possibility of increased intracranial pressure. Cerebrospinal fluid contained 39 mg per cent protein and 563 erythrocytes and 3 lymphocytes per cmm.

Course.—Because of an upper respiratory infection, a scheduled pneumoencephalogram was cancelled, and the child was discharged on February 14, 1958. He was readmitted thirteen days later, at which time his head circumference was 50 cm., and his anterior fontanelle was concave and pulsating.

In preparation for a pneumoencephalogram, he was anæsthetized by open drop vinethine and ether. In the sitting position the CSF level in the manometer was at the level of the inion. Pneumoencephalography revealed some air in the subdural space, a large amount in the subarachnoid space, and a very small amount of air in the ventricles. The study was not satisfactory, but was interpreted as showing diffuse increase in the size of the cerebral sulci and dilatation of the ventricular system, indicative of both grey and white matter atrophy of the brain. Cardiac arrest occurred during the course of the procedure, and following thoracotomy and unsuccessful resuscitatory measures the child died.

Autopsy (N–58–38, D–615) was limited to removal of tissue for microscopic study only, and was performed by Dr. A. Moure. The body weight was 15·5 lb. and the length 63 cm. The legs and arms were short in relation to the body size, the thighs measuring only 9 cm. in length. The calvarium was of normal thickness. No changes were seen in the dural sinuses or hypophysis. The posterior fossa appeared to be smaller than usual, at least in comparison to the rest of the skull, the volume from foramen magnum to lateral sinuses being 52 ml.

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The weight of the fresh brain was 1,060 grammes, the cerebral hemispheres contributing 940 grammes and the cerebellum and brain-stem 120 grammes. There was a striking enlargement of the cerebral hemispheres, but the brain-stem and cerebellum did not appear abnormal. The leptomeninges were transparent. The convolutional pattern appeared normal, and there were no tentorial pressure grooves or cerebellar pressure cone. The vessels at the base of the brain were normal.

Coronal cut surfaces of the fresh brain revealed the lateral and third ventricles to be normal, and no changes were seen in the grey or white matter or in the basal ganglia. There was, however, a moderate dilatation of the aqueduct of Sylvius. Horizontal cut sections through the brain-stem and cerebellum revealed no other lesion.

Final pathologic diagnoses included achondroplasia and bilateral marked patchy atelectasis.

Case 3.—This 5 10/12 years old white female had been recognized as having achon droplasia at birth. She had been in good health until eight months before admission, when she developed fever and pyuria with frequent episodes of fever up to 104°. Approximately one month prior to admission to the Texas Children's Hospital the peripheral white blood count was 3,000 cells per cmm. with a relative lymphocytosis. For five days prior to admission she had two daily spikes of fever.

Family and past history.—There was no evidence of achondroplasia in the family. Development had been normal.

Physical findings.—Crown-heel length was 84 cm. The head to symphysis distance was 53 cm., symphysis to ankle 28 cm., arms 29 cm. and legs 33 cm.

The lymph nodes were generally small, arm, non-tender, and freely movable. The liver was palpable 2·5 cm. below the right costal margin. The spleen was palpable 1 cm. below the left costal margin.

Laboratory data.—Hæmoglobin was 9·8 gramme per cent and hæmatocrit 31 per cent. The white blood cell count was 7,500 with 12 per cent polys., 10 per cent bands, 77 per cent lymphocytes, and 1 per cent monocytes. Reticulocyte count was 0·6 per cent, and the total platelet count was 352,000. A bone-marrow aspiration was interpreted as acute leukæmia.

Course.—The child was treated with hydrocortisone. On the second hospital day an otitis was identified and she was treated with penicillin. After four days of cortisone therapy, the white blood cell count had dropped to 2,350 with 52 per cent polys., 2 per cent bands, 45 per cent lymphocytes, and 1 per cent monocytes.

The child was discharged, but was readmitted two weeks later because of fever. At this time she had coarse breath sounds over both lung fields. The liver was palpable 4 cm. below the right costal margin. The spleen was not palpable. Anæmia and leucopenia persisted. She was treated with penicillin, sulfonamides and hydrocortisone. Her fever dropped from 104 to 101 degrees. Ten hours after admission, she had a sudden episode of opisthotonus followed by cyanosis and atony. There was no response to emergency measures, and the child expired, aged 5 11/12 years.

Autopsy (A–59–17) was performed by Dr. E. L. Bigelow. The crown-heel length was 84 cm. The lower extremities and trunk each measured 35 cm. The upper extremities measured 31 cm., and the upper arm 14 cm. The head was 54 cm. in circumference, thorax 51 cm., and abdomen 47 cm. The calvarium was normally formed and was thought to appear large only by contrast with the remainder of the body. The structure of the calvarium was unusual only with regard to the posterior fossa, which appeared markedly flattened, but which measured 84 ml. in volume. The odontoid process bulged into the foramen magnum on the right side (fig. 2).

The weight of the fresh brain was 1,440 grammes. After fixation in 10 per cent

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formalin, the brain weighed 1,600 grammes, the brain-stem and cerebellum contributing 195 grammes. The external and cut surfaces of the brain were within normal limits. The ventricular system was of normal size.

Microscopically, the bone-marrow was very hypocellular with a few fibroblasts, a small number of granulocytes and a rare megakaryocyte. The lymph nodes were moderately depleted of cells. There was no evidence of leukæmic infiltration, and it was assumed that the infant expired in remission from her leukæmia.

Microscopic examination of a line of ossification revealed a normal degree of maturation but with a relative excess of appositional growth.

The cause of death was not apparent. The possibility was considered that a relative increase in intracranial pressure resulted from the steroid therapy, which, in association with the flattened base of the calvarium resulted in medullary enroachment and subsequent demise; but there was no gross evidence of increased intracranial pressure.

Case 4.—This infant male was delivered after 38 weeks gestation to a 40-year-old gravida V, para IV, white mother. The infant was mottled and cyanotic at birth and was found dead in his crib two hours later.

Autopsy (C–59–58; D–876) was performed by Dr. E. L. Bigelow. There was a marked disproportion between the size of the extremities and that of the trunk. The crown-heel length was 38 cm. and the crown-rump length 33 cm. The hands were short and wide. The frontal bones of the skull were prominent. The circumference of the head was 38·5 cm. while that of the thorax was 30 cm., and of the abdomen 36·5 cm. There was a moderate enlargement of both the liver and spleen in comparison to the weights of a normal newborn infant.

The fresh brain weighed 460 grammes. The posterior fossa appeared flattened and measured 16 ml. in volume. The cervical spinal cord was tightly surrounded by the foramen magnum (fig. 3). Multiple horizontal sections of the cervical vertebral column with the spinal cord *in situ* revealed this disproportionate compression of the cord by the cervical vertebræ throughout (fig. 4).

Examination after fixation of the brain revealed the cerebrum to be enlarged in relation to the cerebellum. The entire brain weighed 560 grammes, the cerebellum and brain-stem contributing 30 grammes. There were numerous microgyri superimposed on the usual convolutions of the temporal lobe. On coronal sections (fig. 5) there was a slight enlargement of the frontal and left occipital horns of the lateral ventricles. There was a wide deep inferior temporal sulcus which deformed the temporal lobe by its extension almost to the ventricle. Horizontal sections of the brain-stem and cerebellum revealed that the aqueduct of Sylvius was slightly enlarged, while the fourth ventricle was normal in size.

Case 5.—This premature achondroplastic baby boy, the result of a third pregnancy of a 27-year-old negro woman, was born at the Hermann Hospital after six hours of labour at an estimated gestational age of 32 weeks. He weighed 4 lb. 4 oz., was slow to breath and cyanotic, and lived only two hours.

Autopsy (A–59–322) was performed by Dr. N. R. Lewis. The baby weighed 1,980 grammes and measured 30 cm. (crown-rump) and 35 cm. (crown-heel). There was a left parieto-occipital cephalohæmatoma. There were tears in the tentorium cerebelli and falx cerebri, but no hæmorrhages were seen. The spinal cord filled the foramen magnum, but autolysis was advanced so that the significance of this remained in doubt. The posterior fossa was long anteroposteriorly and narrow transversely. It seemed shallow and could contain only 4·5 ml. of fluid. The fresh brain weighed 420 grammes. No evidence of internal hydrocephalus was noted.

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Quantitative Analysis of Cases of Achondroplasia

Initially the most impressive aspect of these cases was the absence of hydrocephalus and the presence of megalencephaly as the cause of the enlarged heads. A graphic representation of the relationship between age and head size and brain weight was prepared (fig. 6). Also included in fig. 6 are data on other published cases (Collmann, 1901; Dandy, 1921; Gruber, 1936; Johannessen, 1898; Lucksch, 1944; Parhon, *et al.*, 1905;

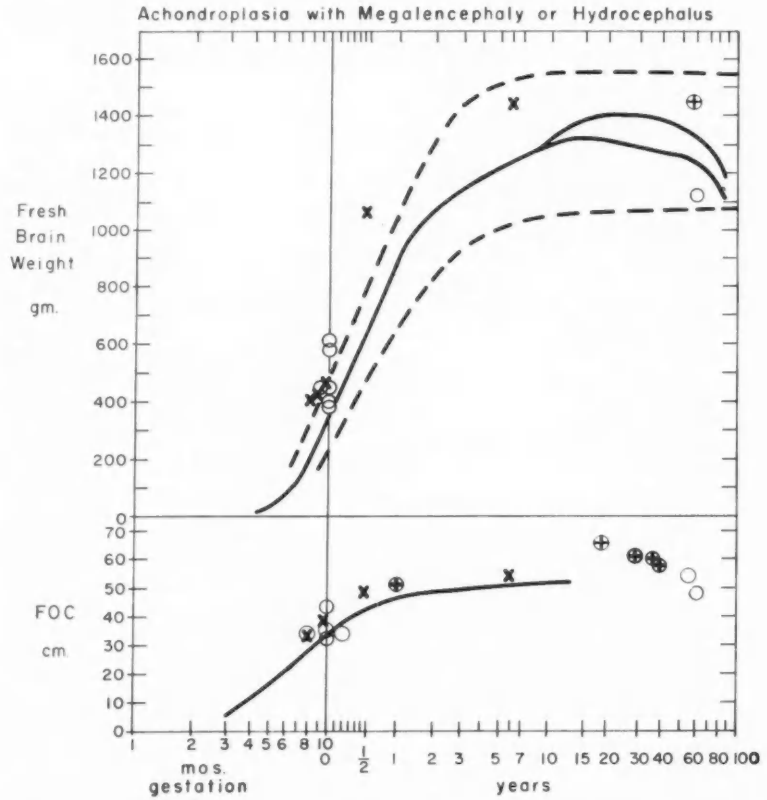

FIG. 6.—External head (fronto-occipital) circumference (FOC) and weight of the fresh brain in relation to age. Normal averages for FOC (Dekaban, 1959; Myers, 1926; Scammon and Calkins, 1929; Vickers and Stuart, 1943; Westropp and Barber, 1956) or brain weight (Coppoletta and Wolbach, 1933; Dunn, 1921) are in solid lines. Dashed lines include range of normals in Houston. X's represent presently reported cases of achondroplasia. Circles represent cases from the literature (*see* Table I), plus marks indicating hydrocephalus.

Parhon and Schunda, 1913; Potter, 1952; Russell, 1949; Singleton, 1960; Spillane, 1952; Welter, 1936) supplemented by data generously supplied by Dr. Potter (1958). Not included are the many cases in which only the external appearance of the head was recorded without evidence for or against ventricular dilatation (hydrocephalus). The range of normal fresh brain weights in Houston, Texas, at the present time is remarkably symmetrical to the averages reported at least a generation ago in New England (Coppoletta and Wolbach, 1933) and Germany (Roessle and

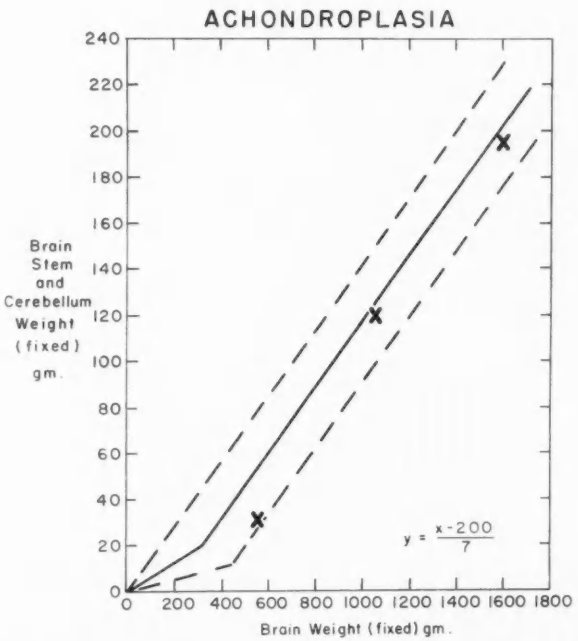

FIG. 7.—Relation between weights of brain-stem and cerebellum and of the whole brain after fixation. The dashed lines include the range of normals. X's represent cases of achondroplasia.

Roulet, 1932). It is evident that eleven of the sixteen heads are above average size, and that, while only six of the thirteen brains are definitely above the upper range of normal weight, all but one are above the average weight. Whether cerebral œdema, due to respiratory failure and anoxia such as reported in one case (Jenkinson and Kinzer, 1941), could account for this increase in weight is difficult to prove, except that such increases in weight of the brain have not been observed in other cases coming to

autopsy during this same period and presumably accompanied by comparable degrees of anoxia.

Since the impression was repeatedly gained that the brain-stem and cerebellum were small in comparison to the rest of the brain, studies were undertaken of the ratio of weights of parts of the brain. This was most easily done after fixation in 10 per cent formalin for two to three weeks, the mid-brain transected, and the weight of the brain-stem and cerebellum compared with the weight of the whole brain (fig. 7). Surprisingly the impression of a disproportion could not be confirmed.

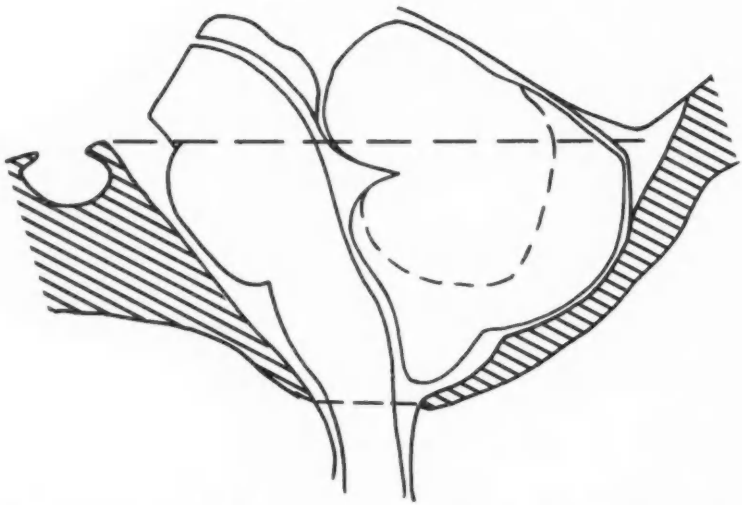

FIG. 8.—Sketch of the posterior fossa in mid-sagittal plane. The volume of the bony portion can be measured *post mortem* with water from the level of the foramen magnum to the level of the lateral sinuses (dashed lines), but the superior portion beneath the tentorium cerebelli is excluded.

In view of the theory that the posterior fossa is small in achondroplasia (Dandy, 1921; Russell, 1949), and in view of the proportionate megalencephaly which had just been demonstrated, it next was of interest to determine the volume of the posterior fossa (figs. 8 and 9) and to compare this with the weight of its contents (figs. 9 and 10). It is evident that the volume of the bony posterior fossa is normal for the patient's age but is relatively small for its abnormally large contents, the brain-stem and cerebellum.

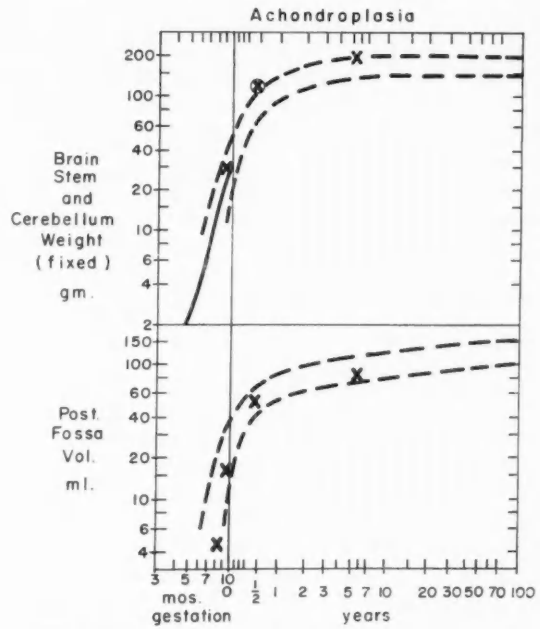

FIG. 9.—Volume of bony posterior fossa and weight of the formalin-fixed brain-stem and cerebellum in relation to age in cases of achondroplasia (X's) in comparison with range of normals (between dashed lines). Case 2 (circle) could be weighed only fresh. The solid line for the weight of the premature brain-stem and cerebellum is from Table 41 of Dunn (1921) corrected for age from Table II of Hamilton *et al.* (1945).

DISCUSSION

Achondroplasia is a specific disturbance in enchondral bone formation (Knötzke, 1929; Luck, 1950). This disturbance apparently arises spontaneously as a mutation and is then transmitted as a dominant gene (Mørch 1941; Potter and Coverstone, 1948). Although there have been many studies of the skull and deductions made concerning the brain in achondroplasia, few studies of the brain itself have been reported. In his analysis of the large brachycephalic head, a characteristic of 78 per cent of achondroplastics (Mørch, 1941), Dandy (1921) offered good reasons for rejecting only relative enlargement, thickening of the skull (Cestan, 1901; Méry, 1902), and tribasal synostosis which accounts only for the receding bridge of the nose (Collmann, 1901). Dandy (1921) settled upon internal hydrocephalus which he demonstrated by ventriculography in one case and strongly suspected on clinical grounds in another case. Although he predicted that "the large heads of other recorded cases presumably have a similar cause," and that "when untreated, a defective brain, it would seem, inevitably

results," it is now well known that within wide limits intellectual ability is not related to the size of the head (Laurence, 1958), the size of the cerebral ventricles, or the weight of the brain. Although the limits are not easy to define precisely, such a generalization appears to apply not only to persons with normal skeletal development but also to persons with achondroplasia.

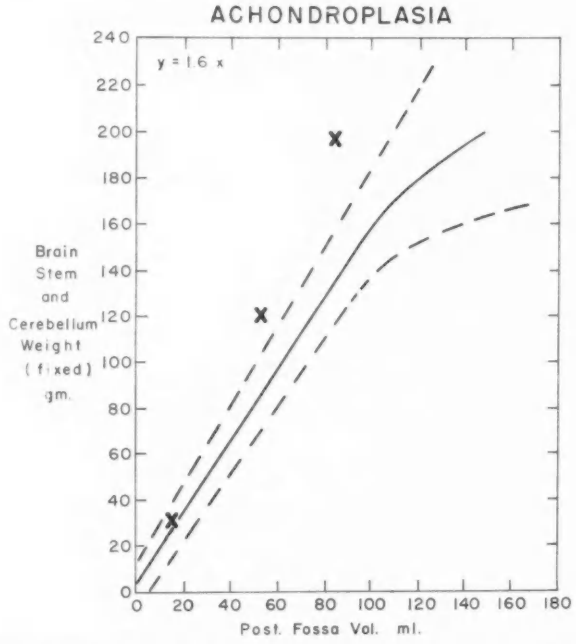

FIG. 10.—Relation between volume of bony posterior fossa and weight of the brainstem and cerebellum after fixation in cases of achondroplasia (X's). The dashed lines include the range of normals.

The mentality in achondroplasia is generally normal (Apert, 1901; Fussell *et al.*, 1909; Jenkinson and Kinzer, 1941; Lugeol, 1892; Mørch, 1941; Vilaire-Cabèche, 1902) or not seriously defective (Porak, 1890). Mørch (1941) felt that the work capacity was normal if the patient was given the opportunity. Only one of his cases was considered to have low mentality. However, no psychological tests were given, so that his observations need not be considered significantly different from those of Morris (1953), who found 5 cases of mental retardation out of 16 cases of achondroplasia in a population of 546,500. In an excellent review of the early literature concerning 42 cases of achondroplasia Parhon *et al.* (1905) were

impressed by the incidence of mental deficiency, present in 9 of 16 cases in which mental ability was noted, and by the direct correlation between the degree of externally measured macrocephaly and the degree of mental deficiency. They pointed out that the only 2 cases with superior intelligence were girls 10 years old with normal head circumferences of 51 and 52·5 cm. They did not mention hydrocephalus, megalencephaly or the post-mortem state of the brain except in their second case, where evidence was found of chronic diffuse meningoencephalitis and atherosclerosis. Most defective was the case reported by Dide and Leborgne (1904) with an FOC of 62 cm. Subsequently Zosin (1910) reported a case with mental deficiency but an FOC of only 54·5 cm. Dandy (1921) reiterated that "the intellect is inversely proportional to the size of the head," enlargement of which was attributed only to hydrocephalus, but Spillane (1952) reported 2 cases of achondroplasia with hydrocephalus but with normal mentality and another case with hydrocephalus and mental deficiency, and Lucksch (1944) reported a case of an achondroplasic idiot without hydrocephalus or other gross abnormality of the brain. Probably the safest conclusion at present is that reached by Leriche (1904), who did not correlate intelligence and head size but stated that both varied considerably and independently in achondroplasia. Further evidence against the correlation of mental deficiency and hydrocephalus in general was offered by Edinger (1899) who cited Perls as suggesting that many intellectually eminent men represented cases of arrested hydrocephalus. Unfortunately few systematic studies have been made, and the proof of these conclusions is far from clear cut.

One of the greatest problems lies in the definition and significance of *megalencephaly*. It is relatively easy in theory to define *megalencephaly* or *megalobarencephaly* (Wohlwill *et al.*, 1959) as increased weight of the brain in comparison to the mean weight (+ its standard error) of the brain for each age and sex (Coppoletta and Wolbach, 1933; Roessle and Roulet, 1932), but in practice it is not quite so easy. Needless to say, the weights are of the fresh organ, and weights obtained after embalming of the body or after fixation of the brain are almost meaningless, since the gain in weight is not predictable. Furthermore, patients tend to die in a state of variably severe hypoxia which may lead to cerebral œdema, one of the most difficult conditions to recognize after the brain has been removed post mortem. Assuming that the skull and scalp are not abnormal, and having eliminated hydrocephalus, one may use the circumference of the head and the weight of the brain as two indications of true megalencephaly. But having determined that megalencephaly is present in a particular case, one must go further to understand its significance since it represents a heterogeneous group of conditions which may be considered one of the many types of congenital or acquired "limited" asymmetries (i.e. limited

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TABLE I.—SUMMARY OF AVAILABLE NEUROPATHOLOGIC DATA IN ACHONDROPLASIA

		Fresh				
Reference	*Age*	*Body wt.* (*g.*)	*brain wt.* (*g.*)	*FOC* (*cm.*)	*Hydro-cephalus*	*Megal-encephaly*
Case 1	8 mos. gest.	1,785	400	33	±	+
Case 5	8 mos. gest.	1,930	420		0	+
Spillane (1952)	8 mos. gest.				0	
Collmann (1901)	8 mos. gest.			34·5	±	
Cohn and Weinberg (1956)	9 mos. gest.	1,920			+	
Cohn and Weinberg (1956)	„ „(twin)	1,700			+	
Potter (1958)	premature	1,930			+	
Jenkinson and Kinzer (1941)	premature				0[1]	
Case 4	newborn		460	38·5	0	+
Welter (1936)	newborn	2,400		35–42	+	
Russell (1949)	newborn			43·5	+	
Draps (1952)	newborn				+	
Potter (1958)	newborn	2,420	450		0	±
Potter (1958)	newborn	2,885	615		0	+
Potter (1958)	newborn	2,950	384		0	0
Potter (1958)	newborn	3,000	448		0	±
Potter (1958)	newborn	3,060	579		0	+
Potter (1958)	newborn	3,240	398		0	0
Potter (1958)	newborn				0	
Potter (1958)	newborn				0	
Potter (1958)	newborn				0	
Potter (1958)	newborn				0	
Knötzke (1929)	newborn				±[2]	
Meyer (1924)	newborn				+	
Meyer (1924)	newborn				+	
Gruber (1936)	newborn	3,700		32·6	±	
Cohn and Weinberg (1956)	newborn	3,200			+[3]	
Johannessen (1898)	2 mos.			34	0	
Case 2	5½ mos.		1,060	50	0	+
Singleton (1960)	1 year			51	+[4]	
Case 3	6 years		1,440	54	0	±
Dandy (1921)	19 years			65	+	
Broggi (1933)	21 years[5]				0	
Spillane (1952)	29 years			61	+	
Spillane (1952)	37 years			60	+	
Spillane (1952)	40 years			57·5	±	
Parhon *et al.* (1905)	54 years			54	0[6]	
Parhon and Schunda (1913)	57 years		1,450		+[7]	±
Lucksch (1944)	60 years[8]		1,120	48	0	0
MacCallum (1915)	75 years				+[9]	

[1] "Marked œdema and hyperæmia."

[2] Marked external hydrocephalus also.

[3] Aqueduct not identifiable.

[4] "Chronic arachnoiditis," gross diagnosis at surgery.

[5] Astrocytoma of tuber cinereum.

[6] Chronic diffuse meningo-encephalitis.

[7] "une dilatation moderée des ventricules latéraux."

[8] Idiot.

[9] Marked cortical atrophy (? *ex vacuo*).

to the nervous system) recently reviewed by Ward and Lerner (1947). The following classification is proposed:

(1) "Simple" or "primary": excessive weight of the brain, which is otherwise grossly and microscopically normal (Apley and Symons,1947; Wiglesworth and Watson, 1913). Whether hyperplasia or hypertrophy (Campbell, 1905) of cellular elements is present is difficult to determine, but such cases probably represent merely an upwards extension of the distribution of weights of the brains of the normal population (Wilson, 1934). This group has not always been clearly distinguished from group 2 below, so that few reliable studies of the mental capacity of such cases have been recorded. Suffice it to say that high, normal, and low I.Q.s with or without epilepsy have been reported to occur with megalencephaly in which post-mortem study has not revealed sufficient abnormality to classify the case in group 2 below (Brain, 1937; Jacob, 1956; Josephy, 1936; Ostertag, 1956; Wiglesworth and Watson, 1913).

(2) "Secondary": in addition to the excessive weight the brain has other gross and/or microscopic abnormalities, which may be quite varied, and which are frequently associated with epilepsy and/or mental retardation (Haberlin, 1906; Jacob, 1956; Ostertag, 1956; Wilson, 1934; Wilson, 1954). The various abnormalities reported (Jacob, 1956; Josephy, 1936) include polymicrogyria, poor lamination of the cerebral cortex, disproportionately thick cortex and thin white matter or "innere Dysharmonie" (Jacob, 1956), leucodystrophy, protracted cases of amaurotic family idiocy (Aronson *et al.*, 1955), subpial deposits of pecular materials (Crome, 1953; Stevenson and Vogel, 1952; Wohlwill *et al.*, 1959), various heterotopias, cerebellar hamartomas (Duncan and Snodgrass, 1943; Hallervorden, 1959), and diffuse gliosis, especially of the white matter (Campbell, 1905), sometimes with neoplastic tendencies or diffuse glioblastosis (Ferraro and Barrera, 1935; Weil, 1933).

The few data concerning the state of the brain in 40 reported cases of achondroplasia are summarized in Table I. 6 definite cases of megalencephaly are recorded with 4 others of slight degree. Only 3 brains of normal weight complete the total of 13 cases for which the weight of the brain has been recorded, and one wonders how many cases have been overlooked by the simple omission of weighing of the brain. So far as can be determined, 4 of the presently reported 5 cases belong to the first group of megalencephaly ("simple" or "primary"), as do probably the other cases of megalencephaly with achondroplasia which Potter (1958) has examined. Two of the presently reported cases (Nos. 2 and 3) lived long enough to suggest that the megalencephaly was compatible with normal mental development. Case 4, however, belongs to the second group of megalencephaly ("secondary"), since microgyria and abnormal fissures were present in the temporal lobes (fig. 5). In the absence of systematic studies it is impossible to estimate the incidence of megalencephaly or of its various types in achondroplasia.

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The pathogenesis of megalencephaly can be only speculative. It is of historical interest that Jansen (1912*b*) rejected a colleague's suggestion "that the malformation of the brain might be explained by a primary hypoplasia . . . of the basis cerebri, or also by a primary hyperplasia of its hemispheres" because of the lack of a ready explanation: "the mechanical malformations of the face and the foramen would need to be explained as well as the hyperplasia or the hypoplasia of the brain." One may suggest that growth hormone, which cannot act upon the genetically and, therefore, probably chemically abnormal growing bones, becomes available in excessive amounts and stimulates the brain to grow excessively. The more or less selective effect upon the nervous system may be a result of the fact that the neonatal nervous system has one of the most rapid rates of growth. Against this is the observation by Jansen (1912) that the pituitary gland is decreased in size in the non-viable severe cases. It is unlikely that slight hydrocephalus stimulates the formation of excessive neural tissue, since such has not been observed in other types of hydrocephalus (Alvord, 1960; Home, 1814). The association of megalencephaly and achondroplasia in man is interesting, especially since Pearce and Brown (1945) observed a 4·6 per cent increase in weight of the brain in hereditarily achondroplastic rabbits as compared to normal siblings. If the gastro-intestinal mass were first discounted, the increase in brain weight was still much greater (41·6 per cent) than in the normal siblings. The absence of lesions in the brain of achondroplastic pups reported by Mather (1956) is not sufficiently detailed for further comment. The opposite, microcephaly, has also been produced by Karnofsky *et al.* (1950) in chick embryos which developed many of the features of achondroplasia following injection of thallium on the fourth day of incubation; the head and brain in these chicks were smaller than in normals. It is interesting to speculate what relationship these observations may have to the case of achondroplasia and microcephaly described by Potter (1952). Perhaps there is more than a single cause of achondroplasia in man also.

Also in Table I are recorded 20 cases of hydrocephalus, 3 of which were only slight. 20 patients are known not to have had hydrocephalus. Omitted from Table I are all cases in which the diagnosis of hydrocephalus was made on the basis only of study of the skull or of the external appearance of the patient. In the absence of systematic studies it is impossible to estimate the incidence of hydrocephalus in achondroplasia, but it seems clear that cases with hydrocephalus have attracted more interest than cases without hydrocephalus and that this summary of the literature gives a falsely high estimate. Previous opinions have varied widely: Luck (1950) stated that "virtually all achondroplastics have a slight degree of hydrocephalus, and this is a factor in the actual and relative enlargement of the head," but he offered no data confirming his belief. On the basis of a personal examination of 86 living and 22 recently deceased achondroplastics

in Denmark, Mørch (1941) stated that the external appearance "may remind of hydrocephalus, although it is due to this lesion but extremely seldom." Unfortunately he also presented no ventricular contrast studies nor descriptions of the brain *post-mortem* to corroborate this impression. Marie (1900) described the large head, "with all the appearance of hydrocephalus, but without an autopsy one cannot say if the ventricles are dilated as in true hydrocephalus" (our translation). Potter (1952) noted that the head, already enlarged at birth, "may become so large during the first few months as to delay sitting and walking. This is sometimes mistaken for hydrocephalus, but the amount of fluid in the head almost never increases."

What is the pathogenesis of the hydrocephalus when it does occur in achondroplasia? Certain cases present anomalous features: possible hydrocephalus *ex vacuo* with marked cortical atrophy (MacCallum, 1915), possible chronic leptomeningitis (Dandy, 1921; Singleton, 1960), coexistent external hydrocephalus (Knötzke, 1929), and stenosis of the aqueduct of Sylvius (Cohn and Weinberg, 1956). Such variety does not permit generalization, but theories as to the cause of hydrocephalus in achondroplasia have included the following: shortening of the basis cranii (Jansen, 1912b; Meyer, 1924) with kinking of the aqueduct of Sylvius and obliteration of the basal cisterns (Dandy, 1921) or compression of the fourth ventricle (Jansen, 1912); small posterior fossa (Russell, 1949); synostosis of sagittal and coronal sutures (Dietrich-Weinnoldt, 1926); and narrowing of the jugular foramina with increased cerebral venous pressure (Welter, 1936). The last mechanism has also been held to account for hydrocephalus in osteopetrosis (Nussey, 1938). Porak (1889) noted the association of hydrocephalus and synostosis of the basis cranii, but very carefully stated his belief that they were independent entities and not causally related. Unfortunately in his only autopsied case the brain and spinal cord were not examined. From the data of the present cases it would seem that compression of the fourth ventricle or of its exit-foramina could result from the relative smallness of the posterior fossa due to the megalencephaly. It may be mentioned that in the Arnold-Chiari malformation, although megalomyelia (hyperplasia) is present (Barry *et al.*, 1957), almost the reverse occurs: small posterior fossa and hypoplasia of the cerebellum (Alvord, 1960).

One final point remains for discussion, namely, the effects of achondroplasia upon the spinal cord. Compression of the spinal cord occasionally produces paraplegia (Donath and Vogl, 1925; Spillane, 1952; Vogl and Osborne, 1949) and is due to the premature synostosis especially of the pedicles, which are unusually short. The anteroposterior diameter is markedly narrowed, sometimes less than 1 mm. clearance obtaining (Vogl and Osborne, 1949). Although the foramen magnum may be normal (Spillane, 1952), it frequently is narrow (Cohn and Weinberg,

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1956; Collmann, 1901; Jansen, 1912; Knötzke, 1929; Luck, 1950; Potter 1952; Singleton, 1960), due to an exaggerated development of periosteal bones (Draps, 1952; Knötzke, 1929), osseous hypertrophy (Cohn and Weinberg, 1956) or "abnormal lip-like protuberances on the lateral and posterior margins" (Potter, 1952). Such narrowing may cause neonatal death (Cohn and Weinberg, 1956; Collmann, 1901; Draps, 1952; Jansen, 1912; Potter, 1952; Singleton, 1960) by obliteration of the epidural and subdural spaces (figs. 3 and 4) with compression of the cervical spinal cord or caudal medulla. As an extreme example Jansen (1912) cited Lampe's observation of the medulla having been compressed to only 2 mm. in anteroposterior dimension. Some idea of the probable frequency of this complication can be gained from the report of Mørch (1941), that of 14 consecutive births of achondroplastic babies eight deaths occurred in the first three days of life and two more in the first year. Further possible explanations for this high mortality have included difficulty in delivering the large head (Porak, 1890) and various extra neural factors, including anemia, immaturity of erythrocytes, pulmonary hypoplasia (Potter, 1952), and general visceral weakness (Fussell *et al.*, 1909). Fig. 2 illustrates another type of abnormality at the foramen magnum, asymmetric indentation and compression by the odontoid process, such as occurs in certain types of basilar impression or platybasia. The combination of megalomyelia—as yet unproven but a likely accompaniment of megalencephaly—and small foramen magnum and vertebral canal in achondroplasia would appear to be a particularly unfavourable combination.

Summary

Because of the interest in hydrocephalus megalencephaly has apparently been overlooked as a possible cause of the enlarged head characteristic of most cases of achondroplasia. 5 consecutive cases of achondroplasia with megalencephaly but without hydrocephalus are presented. 5 other cases of megalencephaly and 20 cases of internal hydrocephalus have been found in a review of the literature, a total of only 40 cases of achondroplasia having been found with specific reference to the state of the brain. Unfortunately the weights of only 13 brains have been recorded, so that further study of more cases is obviously necessary before any conclusions can be drawn from these observations. It is suggested that megalencephaly may represent only part of a general disturbance in growth which may be characteristic of achondroplasia. Evidence is presented that the volume of the posterior fossa is normal for the age of the achondroplastic patient, but is relatively small when compared to the concomitant megalencephaly. No data on the size of the spinal cord are available, but smallness of the foramen magnum and vertebral canal and eccentric indentation of the foramen magnum by the odontoid process may also combine with megalomyeloencephaly to contribute to the high neonatal mortality rate and paraplegia associated with achondroplasia.

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PLATE XLVII

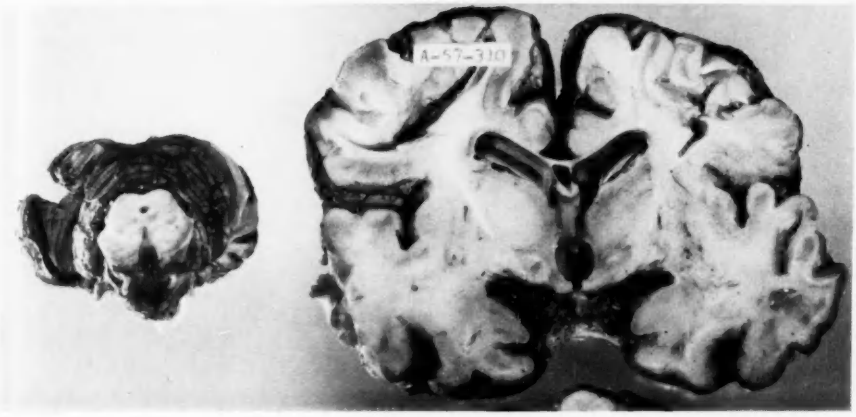

FIG. 1.

FIG. 2.

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FIG. 3.

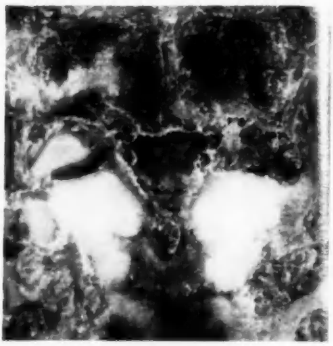

FIG. 4.

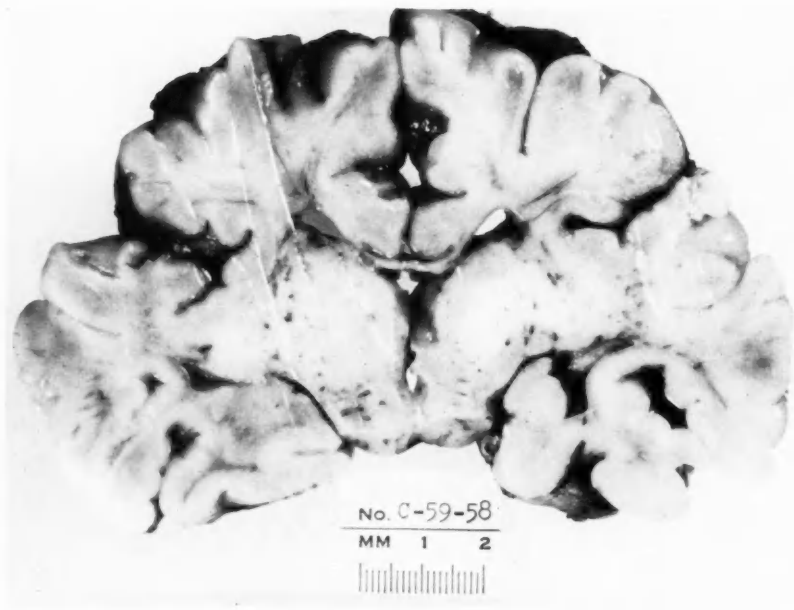

FIG. 5.

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LEGENDS FOR PLATES

PLATE XLVII

FIG. 1.—Coronal section of the cerebral hemispheres and horizontal section of the mid-brain demonstrating the slight internal hydrocephalus which was not sufficient to account for the enlarged head (Case 1).

FIG. 2.—Posterior fossa with asymmetric encroachment upon the foramen magnum by the odontoid process (Case 3).

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FIG. 3.—Posterior fossa with obliteration of the subarachnoid spaces at the foramen magnum about the cervical spinal cord (Case 4).

FIG. 4.—Horizontal section of upper cervical vertebra demonstrating obliteration of subarachnoid and epidural spaces about the spinal cord (Case 4).

FIG. 5.—Coronal section of the cerebral hemispheres demonstrating absence of hydrocephalus and presence of abnormal convolutional pattern in the temporal lobes (Case 4).

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PAROXYSMAL SYMPTOMS IN INTRACRANIAL HYPERTENSION, STUDIED WITH VENTRICULAR FLUID PRESSURE RECORDING AND ELECTROENCEPHALOGRAPHY

BY

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IN an extensive study of the intraventricular fluid pressure (VFP) in patients suffering from intracranial hypertension, Lundberg (1960) was able to identify mainly three forms of variations in pressure. Thus, a great number of patients with a substantial increase of the mean pressure were observed to have large, suddenly appearing "plateau-waves" in their VFP records with peaks of up to about 110 mmHg. Such waves correlated to a typical, more or less pronounced, group of transient clinical symptoms including headache, nausea, slurring of consciousness, hyperpnœa and vomiting, as well as various motor phenomena such as clonic convulsive movements and tonic rigidity in the limbs. He concluded that the attacks seen during plateau-waves were identical to those previously described by several authors under different terms, such as e.g. "cerebellar," or "tonic fits," or "mesencephalic," "decerebrate," "opisthotonic seizures" (cf. Lundberg, 1960, for a thorough review of pertinent literature). The second main form of VFP variations occurred rhythmically with a frequency of 1–2 per minute and was found to be synchronous to periodic breathing. A third form, 6-per-minute waves, had less amplitude and was correlated to so-called Traube-Hering waves in the systemic blood pressure.

The present investigation includes 6 of the patients in Lundberg's (1960) original series in which the EEG was recorded for long periods simultaneously with continuous registration of the VFP. There were two main results of the study. Firstly, it was found that the attacks which accompany plateau-waves of the VFP were not accompanied by epileptic or other forms of paroxysmal cortical discharges in the EEG. Secondly, the small changes seen in the EEG concomitant to the plateau-waves indicated that

some general alteration in cortical functional activity often accompanied the onset, or the cessation of a plateau-wave. On the basis of the results a short discussion of the mechanisms underlying paroxysmal intracranial hypertension will be added.

Material and Methods

Five men and one woman were investigated in a total number of thirteen recording periods which each lasted from one to two hours. All patients, but one, suffered from brain tumours which in 3 cases proved to be malignant gliomas and in 2 of metastatic origin. The sixth patient had a diffuse carcinomatosis of the meninges without any circumscribed intracranial tumour.

The ventricular fluid pressure (VFP) was recorded by means of the method described by Lundberg (1960) with an intraventricular cannula usually mounted in one of the anterior horns and coupled to a strain gauge transducer, the impulses of which were amplified by an ink-writing potentiometer recorder.

The EEG was recorded with conventional technique by means of a Grass EEG machine. Bipolar leads were used which covered both hemispheres symmetrically in two longitudinal lines. Frequent synchronous markings were made in the records in order to identify simultaneous changes in EEG and VFP.

During the recording periods the patients were left undisturbed in their beds and frequent notes were taken of their behaviour, state of consciousness, blood pressure, pulse, and respiratory rate.

Results

In the following a brief summary of the patients' histories will be given, as well as a summary of the findings in the EEG and VFP records.

Case 1.—K. B., a man aged 60 (Case 129 of Lundberg, 1960). *Verified central glioma on left side. Op.: Ventriculo-cisternostomy. Death four weeks post-operatively.*

Four months prior to admission he developed headaches, vomiting and mental clouding. On admission he was disoriented, had a poor memory, and demonstrated rigidity of the neck. There was a paresis of the abducens nerve on the left side, as well as poor vision. Bilateral papillœdema of 4 dioptres was also found. Air studies showed a large central tumour on the left side. Biopsy later demonstrated that it was a malignant glioma. Routine EEG demonstrated a dominant frequency of 7 per second, a general diffuse slow wave admixture and bilateral high voltage delta episodes. The patient was treated by ventricular drainage and later by ventriculo-cisternostomy.

The day after admission a ventricular cannula was inserted into the right anterior horn for VFP control. Basal pressure was elevated to 10–20 mm.Hg and, when the ventricular drain was closed, there were intermittent plateau-waves appearing with an interval of 30 minutes to two hours, lasting about 40 minutes. During the waves the pressure rose to about 60 mm.Hg. Two recordings were made with EEG during 120 (fig. 1) and 180 minutes and four plateau-waves were followed. During each wave the

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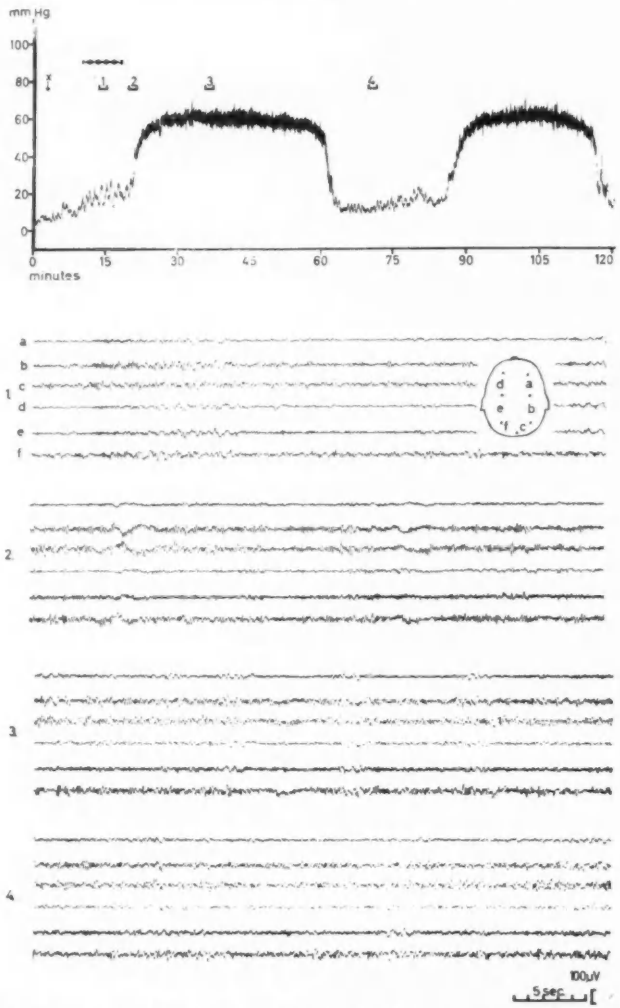

FIG. 1 (*Case* 1).—Records of intraventricular fluid pressure and EEG. Periods to which EEG samples pertain are in the VFP record marked with horizontal bars and numbers in this and subsequent figures. X indicates closure of ventricular drainage. Bar at onset of first plateau-wave indicates period with headache (*see* text).

patient who was lying in his bed, became restless and complained of headache. A flushing of the face was noted as well as increased stiffness of the neck. Sighs, deep breaths and swallowing movements were also noted as well as a general increase of the already marked disorientation and confusion. Later, during other waves with pressures

of up to 70–80 mm.Hg the patient became unresponsive and had clonic convulsive movements in his right arm and hyperventilated. All the symptoms mentioned disappeared when the pressure fell.

The onset of the waves recorded were accompanied by a slight, but clearly evident cortical activation in the EEG consisting of an increased output of alpha activity and a decrease of the slow wave components (fig. 1, sample 2). The EEG pattern during the plateaus was periodically somewhat more active than during the intervals with low pressure, but there were no major changes (fig. 1, sample 3). In this case the systemic blood pressure, the pulse, and the respiration remained uninfluenced at about 120 mm.Hg, 16 per minute, and 70–80 per minute respectively during the plateau waves.

Case 2.—A. M., a man, aged 57 (Case 130 of Lundberg, 1960). *Verified metastasis in left frontal lobe. Bronchial carcinoma. No operation. Gradual deterioration and death.*

Four months prior to admission the patient started to develop attacks of headache, followed by unconsciousness and convulsions in the arms. These attacks were interpreted as true epileptic seizures. A gradual mental deterioration developed with loss of memory, speech difficulties and visual impairment. Roentgen examination of the chest showed a pulmonary tumour. On admission he was torpid and showed stiffness of the neck and bilateral papillœdema. He was moderately aphasic and had a slight right-sided hemiparesis. Carotid angiography showed a tumour in the anterior part of the left hemisphere. Routine EEG showed a great amount of diffuse slow activity which dominated frontally on the left side. The patient's attacks were controlled by ventricular drainage.

Twelve days after admission a ventricular cannula was inserted into the right frontal horn for VFP control. The basic pressure was about 20 mm.Hg. Three recordings were made with EEG of 170, 45 and 30 minutes' duration respectively. During the first, four typical plateau waves were recorded during which the pressure rapidly rose to peak values of 90–100 mm.Hg, later to stabilize for about ten minutes around 80 mm.Hg (fig. 2). No precipitating factor was observed in connexion with the onset of the waves. Every wave was accompanied by a typical attack (fig. 2, bars marked A). The rising phase coincided with groaning, restlessness, purposeless movements and nose scratching. At the peak the patient was unresponsive and did not react to pain. Clonic convulsive movements then developed in the arms with a predominance on the right side. This was followed by a state of tonic flexor rigidity in the arms. The waves were also accompanied by an increase of blood pressure (from 120–130 up to 190–210 mm.Hg), by bradycardia, and, particularly at the end of the wave, by marked involuntary hyperpnœa. As shown in fig. 2 (samples 2 and 3) the clonic jerks induced movement artefacts in the EEG, but no certaine pileptic discharge or other paroxysmal patterns were recorded while the attack lasted. The EEG pattern was only somewhat more active on the whole, showing a slight reduction of the slow wave component than in the intervals with low pressure. The involuntary hyperventilation gave an increase of the slow waves which coincided with the fall of pressure (fig. 2, samples 3 and 4).

Next recording was made ten days later at which time the patient had deteriorated and the EEG had undergone a marked general change. It now showed a pattern of sinusoidal synchronous 2-per-second waves. During this recording the VFP varied rhythmically in series of regular 1-per-minute waves with an amplitude of about 25 mm.Hg. Superimposed were slower waves so that maximal amplitudes of 50 mm.Hg were reached. In the great majority of instances every single peak of the 1-per-minute waves was accompanied by some slight, but clearly seen evidence of behavioural arousal.

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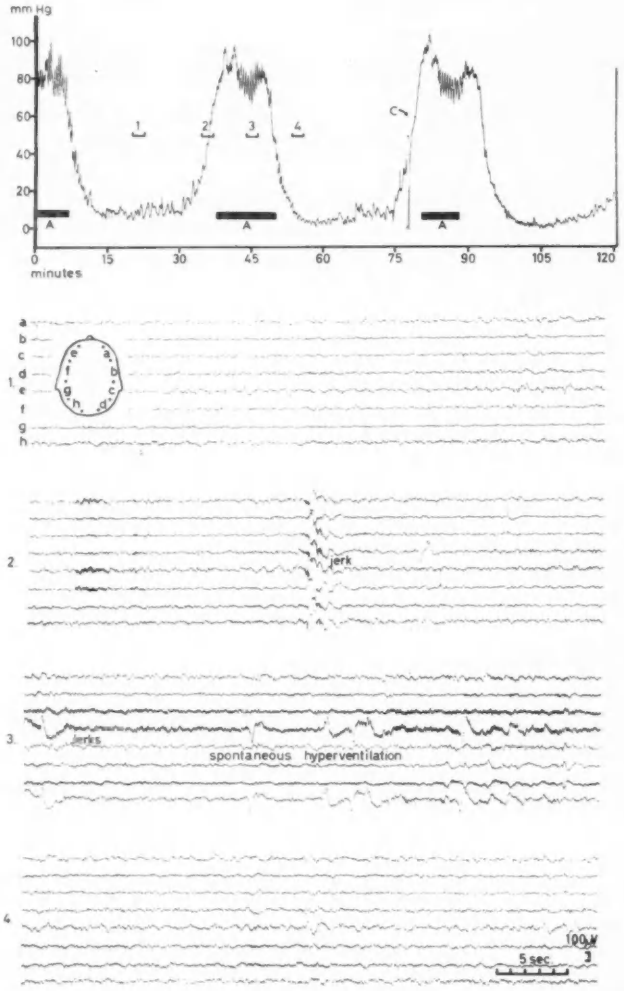

FIG. 2 (*Case* 2).—Records of intraventricular fluid pressure and EEG. Horizontal bars marked A indicate attacks described in text. C indicates calibration. In EEG sample 2 a convulsive jerk was recorded with ensuing movement artefacts. Jerks recorded during sample 3 were of the same type but accompanied by less artefacts (*see* text).

The EEG record also simultaneously showed a short transient period of arousal with depression of the slow wave pattern and the appearance of some alpha (cf. fig. 4). At the last recording a comparatively constant pressure of 25–35 mm.Hg was recorded. There were no significant EEG changes.

Case 3.—A.-G. T., a woman, aged 30 (Case 116 of Lundberg, 1960). ***Diffuse carcinomatosis of the meninges. Bronchial carcinoma. Prolonged drainage of ventricular fluid. Deterioration, respiratory standstill and death after removal of drainage.***

One month prior to admission the patient had attacks in the mornings of headache, nausea and vomiting. On admission stiffness of the neck was found and bilateral papilloedema of 2·5 dioptres. There were no other neurological signs. Air studies showed a normal ventricular system and free passage of gas in the cerebrospinal fluid pathways. Routine EEG showed some bilateral non-focal diffuse delta. Palliation was obtained by ventricular drainage for about six weeks. She had then developed a maxillary metastasis.

Five days after admission a ventricular cannula was inserted into the left anterior (later moved to the right anterior) horn for VFP control. Two simultaneousre cordings of VFP and EEG were made during 270 and 150 minutes each, a few days after admission. During the first the VFP varied in slow regular waves with a frequency of

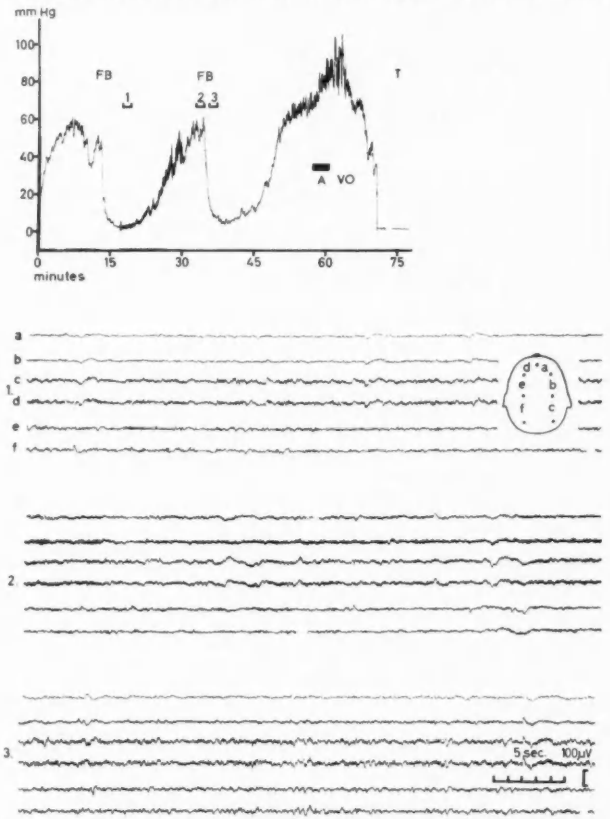

FIG 3 (*Case* 3).—Records of intraventricular fluid pressure and EEG. FB indicates periods of voluntary forced breathing. Bar marked A indicates attack described in text. VO marks vomiting (*see* text). At T ventricular tapping was carried out.

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about 1·5 per hour and peak values of 50 mm.Hg. Four such waves were followed. The onset of the first and the fourth one showed a definitive correlation to signs of arousal in the EEG as well as in the patient's behaviour. At the peaks, when the patient was drowsy, the EEG became less active and showed a pattern typical of light sleep. She showed some restlessness and twitches around the chin were observed occasionally. Such phenomena were accompanied by arousal phenomena in the EEG of the K-complex type and the appearance of some alpha activity. There were no cortical spike potentials simultaneously with the facial twitches.

At next recording the VFP variations were larger (fig. 3 shows end of recording period). The pressure rose in waves to higher and higher levels. The patient was instructed to hyperventilate (fig. 3, marked by FB) when 60 mm.Hg had been reached. After only about 5 deep breaths, there followed a decrease of pressure down to 0–5 mm.Hg. When the pressure was allowed to rise further the patient became unconscious (fig. 3, bar marked A); she then hyperventilated involuntarily and vomited (fig. 3, Vo). (Other similar high waves were accompanied by clonic-tonic convulsive movements.) The EEG was recorded until a pressure of 70 mm.Hg was reached. An

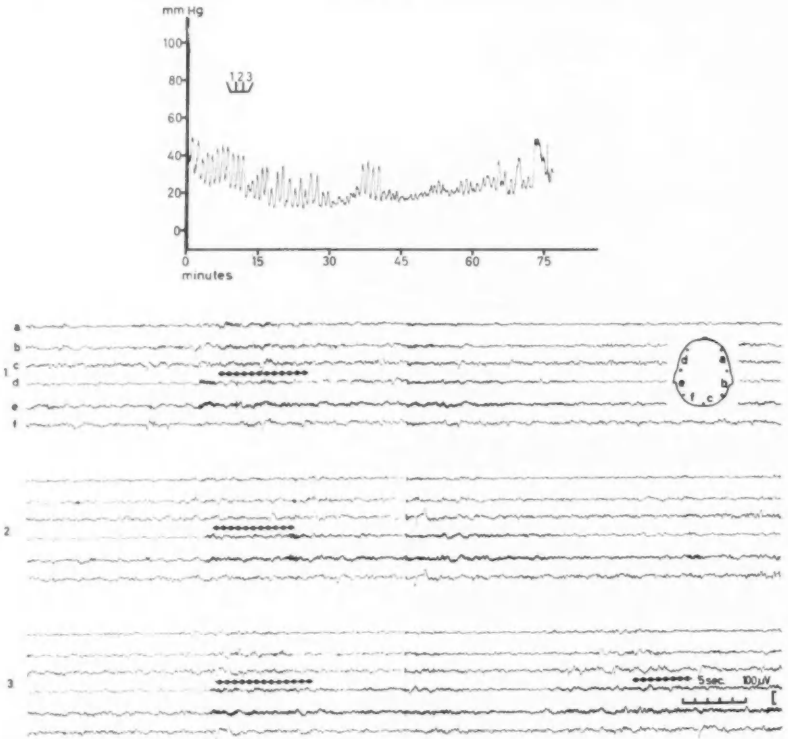

FIG. 4 (*Case* 4).—Records of intraventricular fluid pressure and EEG. Samples 1, 2 and 3 are consecutive. During the corresponding period three large and one small peaks of the "one-per-minute" waves were recorded. These peaks coincided with subtle arousal signs in the EEG. Further description in text.

increased amount of muscle artefacts were recorded but no other change was seen. Voluntary hyperventilation was accompanied by an increased amount of slow waves in the EEG (fig. 3, samples 2 and 3).

Case 4.—O. H., a man, aged 53. *Malignant renal tumour with multiple pulmonary and cerebral metastases.*

One month prior to admission the patient started to have attacks of dizziness, nausea and a slight weakness of his right arm. Chest X-ray in another hospital showed pulmonary metastases. On admission the patient was confused and had a slight paresis of his right arm, a right-sided hemianopia and bilateral papillœdema of 4 dioptres. Neuro-rœntgenological examination demonstrated the existence of multiple tumours in the left hemisphere. Routine EEG showed a marked diffuse delta activity and depression of the alpha, especially on the left side. There were no focal abnormalities. The patient's symptoms were controlled by ventricular drainage.

EEG and VFP were recorded on three occasions. On the first, the basic pressure was 20 mm.Hg and the pressure varied regularly in 1-per-minute periods up to 60 mm.Hg for the first half of the recording period. These waves were accompanied by synchronous periodic breathing and drowsiness. Later the patient was awake and there were no 1-per-minute waves. There were no significant changes in the EEG. During the second recording the VFP also showed 1-per-minute waves initially accompanied by some slight EEG arousal on each peak. The VFP record then changed into a series of four plateau-waves reaching 70 mm.Hg in height and lasting about 15 minutes. During the plateaus the patient became restless in his bed, rubbed his nose and took several deep breaths. These peaks were accompanied by an increase of the dominant postcentral EEG frequency from about 6 to about 9 per second and some decrease in the amount of slow waves. During the last recording period series of regular 1-per-minute waves were recorded in the VFP. Their amplitude was up to 20 mm.Hg and they occasionally reached peaks of up to 50 mm.Hg (fig. 4). During long periods every peak was accompanied by a slight movement of the drowsy patient and he was observed to clear his throat and to swallow once or twice. Every similar event was accompanied by slight signs of increased alpha output in the EEG (fig. 4).

Case 5.—L. B., a man, aged 38. *Verified glioma of the occipital region on the left side. Op.: Left-sided occipital lobectomy.*

Two weeks prior to admission the patient observed a failure of vision to the right and a weakness of his right arm and leg. On admission a right-sided hemianopia and hemiparesis was confirmed. The patient was confused and suffered from difficulty in calculating. Incipient papillœdema bilaterally was found. Neuro-rœntgenological examination demonstrated an expansivity in the occipital parts of the left hemisphere. Routine EEG showed a dominant post-central activity of 7 per second and a diffuse admixture of 0·5 to 3 per second irregular high voltage delta with a predominance occipitally on the left side. Sixteen days after admission a left-sided occipital lobectomy with tumour resection was made.

Two weeks after admission a ventricular cannula was inserted for VFP control. Basic pressure was 15–20 mm.Hg. During a recording period of 120 minutes two plateau-waves were followed during which the pressure rose in about three minutes to 50–60 mm.Hg. The first wave started immediately after the patient was spoken to, the second appeared in the record without any observable relation to outside stimulation. The plateau-waves were both accompanied by general restlessness, increased confusion, incoherent speech, headache and general irritability. The first wave ceased after a short period of deep spontaneous breathing. The EEG during the two plateau-waves

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showed a slight increase in the slow wave component which also spread more to the right side.

Case 6.—K.-O. J., a man, aged 34. *Central tumour in the right hemisphere.*

Six months prior to admission the patient began to suffer from headache, dizziness, and failure of vision. There was also a staggering gait and a general mental deterioration On admission bilateral papillœdema was found, a bitemporal hemianopia, as well as a slight paresis of the right arm. Neuro-rœntgenological examination demonstrated the existence of a large tumour mass located centrally in the right hemisphere. Routine EEG showed a profuse admixture of 1·5 to 2 per second irregular slow waves which dominated frontally on the left side.

A ventricular cannula was inserted into the right anterior horn for VFP control three days after admission and the VFP was controlled for about one month. Two investigations with EEG were made of 45 and 140 minutes' duration respectively. On both occasions the patient was in a rather torpid state. On the first, the VFP varied between 25 and 50 mm.Hg in an irregular manner. There were no clear changes in the EEG which could be correlated with the VFP variations. During the second recording period three typical plateau-waves in the VFP were recorded in which the pressure rose suddenly from 20–25 up to 65–75 mm.Hg for a period of eight to ten minutes. The first wave followed immediately after the patient's head had been raised for adjustment of his cushion. The waves were combined with a slurring of the mental state of the patient, and some restlessness. There were no definite changes in the EEG which could be correlated with the plateau-waves.

Discussion

Although small, the present material includes repeated observations on the most common variants of paroxysmal symptoms occurring in patients with intracranial hypertension. The thirteen investigations with EEG and VFP recordings covered periods during which 20 large plateau-waves were seen. In some of these (fig. 2) fully developed seizures with clonic-tonic convulsive movements and loss of consciousness developed. During other plateau-waves, usually of less height, the clinical symptoms were not so pronounced, but included headaches, general restlessness, mental clouding, nausea and purposeless movements. Finally, in especially 2 of the cases (Nos. 3 and 4), longer periods of typical 1-per-minute waves were recorded in the VFP (fig. 4). The faster type of waves, the 6-per-minute waves, were also seen, but the techniques used were not considered to have a suitable resolution for an analysis of such waves.

Discussing the clinical symptoms and the EEG findings in the present cases, it should be recalled that at least the 5 cases with proven brain tumours primarily suffered from a more or less severe interference with cerebral functions apart from symptoms created by the increased pressure *per se*. It is evident that the primary disturbance might put an imprint upon the syndrome developing during a paroxysmal increase in the VFP. The investigation has not included an analysis of any such individual differences and the discussion will be limited to two points which seem of a more general interest. Firstly, the absence of marked EEG changes even

in fully developed attacks of cerebral symptoms accompanying plateau-waves will be dealt with. Secondly, some comments based upon the EEG findings will be made as to the possible mechanisms underlying the plateau-waves and the 1-per-minute waves seen in the VFP records.

In contrast to the dramatic clinical symptoms and the events in the VFP records during plateau-waves the concomitant EEG changes, when present, were strikingly small, often only of a subtle nature. This general finding confirms the opinion expressed early by Walter (1937) and Williams (1939) who did not find any correlation between absolute height of the intracranial pressure and EEG abnormalities in their series of patients with brain tumours. Both authors based their conclusions on non-continuous measurements of the cerebrospinal fluid pressure. In the present series it seems especially noteworthy that no epileptic cortical discharges were recorded, not even during the high plateau-waves which were accompanied by loss of consciousness and clonic convulsive movements (fig. 2). This observation, although of a negative nature, would seem to stress further the difference between such attacks and true epileptic fits (with generalized or focal high voltage cortical spike discharges, or other forms of paroxysmal rhythms) which, indeed, may also occur in brain tumour cases. This differentiation is of an immediate clinical interest in view of the separate therapeutic measures involved in the two forms of attacks. Those attacks which accompany the plateau-waves in the VFP are not benefited by common anti-epileptic medication, but are as a rule promptly relieved by tapping of cerebrospinal fluid (*cf.* Penfield and Jasper 1954, and Lundberg, 1960).

Webster and Weinberger (1940), amongst many others, described a series of patients with posterior fossa tumours which suffered from attacks which, according to the description given, most likely must have coincided with attacks of paroxysmal intracranial hypertension of the plateau-wave type. They thought the convulsive phenomena were initiated from the motor cortex rendered ischæmic by the increased pressure. This interpretation would not be compatible with the evidence reported above.

The present EEG findings are more consistent with those theories which postulate some subcortical pathological state underlying attacks of the "cerebellar," "mesencephalic" or "decerebrate" type. Such theories were, as is well known, originated by Hughlings Jackson (1906) and later further elaborated by Penfield and Jasper (1954). The latter authors discussed two possible mechanisms, namely, true epileptic discharge, and "release" due to transection—probably ischæmic—of higher parts of the brain-stem. They favoured the view that most transient attacks of the above type in cases with intracranial hypertension "may be considered epileptic seizures which originate within the brain-stem" (Penfield and Jasper 1954, p. 387).

A paroxysmal epileptic discharge in the brain-stem would, it seems,

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involve the so-called reticular activating system (Moruzzi and Magoun, 1949) creating activation and/or paralysis of function. It is then of interest to note that the attacks concomitant to plateau-waves in the VFP record were often initiated by arousal in the EEG and often accompanied by a lowering of the level of consciousness roughly proportional to the height of the wave. In spite of this, however, the EEG changes were, as mentioned, very moderate and only in Case 5 was the depression of consciousness in the patient accompanied by an increase in the slow wave component of the EEG. This poor correlation between intracranial pressure, level of consciousness, and EEG, confirms fully the above-mentioned findings of Williams (1939). It seems pertinent in this context to point out that both clinical and experimental data have shown that structures in the posterior fossa, both in the brain-stem and in the cerebellum might be seriously interfered with without any major EEG alterations. Thus, Lundervold, Hauge and Löken (1956), in a case of brain-stem atrophy, demonstrated the persistence of a normal EEG with alpha activity in spite of the fact that the patient remained unconscious for a year and a half (cf. also Dawson, Webster and Gurdjian, 1951). Clark and Ward (1949) and Johnson *et al.* (1952) showed in animals that electrographic seizures might be induced in the cerebellum without any major concomitant changes in the electrical activity of the hemispheres.

Taken together these data would not contradict the assumption that paroxysmal symptoms in intracranial hypertension are caused by some disorder probably within the brain-stem. Clinical observations suggest a causal relationship between such paroxysmal symptoms of cerebral dysfunction and the plateau-waves of the VFP (Lundberg, 1960). It remains, however, an open question whether the acute rise and fall in pressure during the plateau-waves might induce true epileptic discharge or some "release" phenomenon in the brain-stem. Suffice it to say, that the assumed disorder of the brain-stem which occurs during plateau-waves seems to involve structures which do not have, or are temporarily disconnected from, an immediate influence upon the electrical activity of the cortex.

Lundberg (1960) found that typical plateau-waves in the VFP occurred only in patients in whom there was primarily a significant increase of the mean VFP level. He thought that these waves pertained to a state in which mechanisms for damping of intracranial pressure variations started to fail. Under such conditions any process, even of a limited nature, tending to increase the intracranial pressure by, *e.g.* a reduction of the cerebral vascular resistance and change of the intracerebral blood pressure gradients, would lead to the precipitation of a sudden paroxysmal increase in pressure within the rigid cranial cavity. Evidence for such a vasomotor mechanism was obtained from (1) observations showing that typical plateau-waves could be induced by increasing the fluid pressure by intrathecal or intraventricular injections of small amounts of oxygen or saline

solution, and (2) from the observation that the onset of plateau-waves were occasionally seen to coincide with arousal reactions or emotional stimulation, i.e. with states assumingly causing some acute increase in cerebral functional activity. There is experimental evidence to show that an increase of cerebral, or more precisely cortical, functional activity leads to an augmentation of the cortical tissue tension of carbon dioxide (Ingvar, Siesjö and Hertz, 1959). This increase may, in its turn, be related to the vasodilatation—and slight volume increase—occurring in the cortex when the activity increases as it does during an arousal reaction in the EEG (Ingvar, 1958).

The cessation of a plateau-wave was often observed to follow, or to coincide with, a short period of spontaneous hyperpnœa developing towards the end of the wave (figs. 2 and 3; Kjällquist, Lundberg and Pontén, 1960). It is a well-established fact that hyperventilation by reducing the arterial carbon dioxide tension induces a cerebral vasoconstriction (Kety and Schmidt 1948; *cf.* Lundberg, Kjällquist and Bien, 1959) which may in some cases explain the critical reduction of the cerebral volume initiating the cessation of a plateau-wave. Examples of hyperventilation effects in the EEG records were given in figs. 3 and 4.

The suggestion that the plateau-waves are due to vasomotor accompaniments to augmented cerebral functional activity are to some degree supported by the present EEG observations. In at least five of the twenty such waves recorded the onset correlated to a period of activation pattern in the EEG with a reduction of the pre-existing slow waves. It was not possible, however, with the present techniques to establish whether the EEG changes in these cases preceded the VFP rise, or the opposite.

In the present discussion of the relation between cerebral vasomotor—and possibly also volume—changes and VFP changes, the phenomenon of "spreading depression" of Leão (1944) might also be mentioned. Several authors have demonstrated that this phenomenon which requires some injury to the cortical tissue, is accompanied by a slowly propagating wave of local vasodilatation and volume increase lasting for several minutes (Marshall, 1959). So far, however, Leão's phenomenon has not been demonstrated with certainty in man, and furthermore, the EEG findings in the present series did not show signs of typical depression of activity or paroxysmal discharges of the type met with in experimentally induced spreading cortical depression.

Rhythmic variations in VFP of the 1-per-minute type occur in states of depressed wakefulness and they are intimately related to periodic breathing (Kjällquist, Lundberg and Pontén, 1960). Several investigations in recent years have stressed the close functional relationship between the neural mechanisms of the brain-stem which are responsible for respiratory regulation and those determining the level of wakefulness and general cortical excitability conditions (Bonvallet, Hugelin and Dell, 1955; Bülow and Ingvar, 1960). It is of interest to note that the peaks of the 1-per-minute waves in fig. 4, which appeared during drowsiness and were syn-

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chronous with periodic breathing, coincided with subtle, but clearly visible arousal effects in the EEG.

The notable lack of more pronounced EEG changes during the often dramatic changes recorded in the VFP have, on the whole, confirmed the view that powerful compensatory mechanisms exist which tend to secure an adequate cerebral blood flow—and, hence, an undisturbed electrical activity in the cortex, in spite of the circulatory hindrances created by an increased intracranial pressure (Noell and Schneider, 1948, Gänshirt, 1957).

Summary

(1) Continuous recordings of the EEG and ventricular fluid pressure (VFP) was carried out during thirteen investigations in 6 patients suffering from intracranial tumours with increased intracranial pressure. The patients showed paroxysmal variations in VFP of the "plateau-wave" type or of the rhythmic "1-per-minute wave" type described by Lundberg (1960).

(2) The EEG was primarily abnormal in all cases. During different types of VFP variations recorded the EEG changes were in general found to be very small. There was a notable absence of cortical epileptic discharges in the EEG during high plateau-waves which were accompanied by loss of consciousness and tonic-clonic convulsive movements, i.e. during attacks of the type described in the literature under such terms as "cerebellar," "mesencephalic," or "decerebrate" seizures. The paroxysmal cerebral symptoms accompanying plateau-waves in the VFP would therefore seem to originate in subcortical (probably brain-stem) structures which do not have, or are transiently disconnected from an immediate influence upon the cortical electrical activity. The present EEG observations further emphasize the difference between, on the one hand, true epileptic seizures, also occurring in cases with brain tumours, and, on the other, attacks coinciding with episodes of paroxsymal intracranial hypertension of the plateau-wave type.

(3) The onset of plateau-waves in the VFP often coincided with an arousal reaction in the behaviour of the patient, as well as in the EEG. The cessation of such waves often coincided with hyperventilation and the appearance of an increased amount of slow waves in the EEG. Both arousal reactions and hyperventilation are known to be accompanied by cerebral vasomotor changes (vasodilatation and vasoconstriction respectively). In cases with critical spatial conditions intracranially, such vasomotor changes could be made responsible for the initiation, respectively the cessation of plateau-waves in the VFP.

(4) The peaks of rhythmic 1-per-minute waves in the VFP usually coincided with slight transient signs of arousal in the EEG. Such waves are synchronous with periodic breathing of the Cheyne-Stoke type and periodic variations of the systemic blood pressure.

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RADIATION MYELOPATHY

BY

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INTRODUCTION

THE appearance of signs of spinal cord disorder in patients with malignant disease usually indicates a metastasis and implies a poor prognosis. Metastatic deposits are not, however, the only cause of neurological symptoms in patients with carcinoma. Various syndromes of carcinomatous neuromyopathy have been identified over the past few years and were recently reviewed in detail (Brain and Henson, 1958). Their relation to malignant disease remains obscure.

When patients who have been treated by irradiation develop signs of myelopathy a further differential diagnosis must be considered. Doubt has recently been cast on the idea that nervous tissue, and in particular the spinal cord, is tolerant to radiation (Warren, 1943) and examples of delayed radiation myelopathy have been reported in the literature (Ahlbom, 1941; Smithers, Clarkson and Strong, 1943; Stevenson and Eckhardt, 1945; Boden, 1948, 1950; Greenfield and Stark, 1948; Jacobsson, 1951; Malamud, Boldrey, Welch and Fadell, 1954; Itabashi, Bebin and DeJong, 1957; Lampe, 1958). Clinical details are in many cases very scanty. The main data of the 38 hitherto reported cases are summarized in Table I.*

Boden (1948) was the first in this country to draw attention to the occurrence of a delayed myelopathy following irradiation. He pointed out that in such cases the symptoms had frequently been ascribed, without adequate proof, to spinal metastases, and that "although the lesion was localized anatomically, the correct inference was not drawn, as the

*Since the preparation of this paper Dynes and Smedal (1960) have reported a further 10 cases of radiation myelopathy. Their report includes necropsy findings in one case and findings at laminectomy in two further cases. The doses of radiation received by the spinal cord in these ten cases are in every case in excess of our proposed tolerance level.

neurologist had not always been aware of the site of the previous irradiation or, indeed, conscious of its implications."

In nearly all reported instances, damage to the cord occurred in the cervical region following irradiation of malignant neoplasms of the nasopharynx, hypopharynx, larynx and tongue—or of cervical lymph nodes involved by Hodgkin's disease or lymphosarcoma. There are only 3 cases on record (Greenfield and Stark, 1948) of irradiation damage to the lumbo-sacral cord. Lesions of the thoracic cord were exceptional, despite the frequent use of radiotherapy for malignant disease of pulmonary or mediastinal origin. We have, in fact, only been able to find two reports of radiation damage in the dorsal region. One occurred at D3–D4 after irradiation of an œsophageal carcinoma (Smithers *et al.*, 1943), the other at D1 following radiotherapy for carcinoma of the thyroid (Boden, 1950). Two of the cases of radiation myelopathy to be described here affected dorsal segments of the cord. One of them is, we believe, the first case to have been reported following irradiation of a bronchial carcinoma.

Clinical Features

Signs of myelopathy may appear within hours or days of rapidly administered high dosage irradiation in animals (McLaurin *et al.*, 1955). This type of reaction has not been reported in man. With the smaller doses used therapeutically, the onset of the myelopathy is usually delayed.

From a survey of the reported cases the following clinical picture emerges. The disease may occur at any age. Symptoms most often appear about a year after irradiation. This latent period may vary, however, from one month to over five years. The onset is insidious and the rate of subsequent progress unpredictable. The more common cervical cases often present with tingling and numbness of the extremities, at times associated with a positive Lhermitte sign. The patients may complain of pain in the neck and shoulders. If at this stage there are no abnormal neurological signs complete remission may occur within a few months (Boden, 1948). Other cases progress to a spastic tetraplegia with gross sensory ataxia (superficial sensation often being less severely involved). Occasionally patients may show a cervical Brown-Séquard syndrome. The disease may become arrested at an early stage. More often it progresses to complete cord "transection" and death. Involvement of the sphincters implies a poor prognosis. The cerebrospinal fluid (C.S.F.) is usually normal, although a slightly raised concentration of protein is occasionally found.

Seventeen of the 38 cases reviewed in Table I died of the effects of the myelopathy within periods ranging from one month to four years from the development of the first neurological symptom. Two patients died of conditions other than myelopathy. In 7 patients the disease apparently

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TABLE I

Author	*Cases*	*Age*	*Sex*	*Lesion irradiated*	*Latent period (in months)*	*Prognosis*	*Reported dose to cord*	*P.M.*
Ahlbom (1941)	4	Not stated		Hypopharyngeal neoplasms	12–24	All tetraplegic within 3 months. All eventually fatal (no further details).	Not stated	Yes (but data very scanty)
Smithers *et al.* (1943)	1	61	M	Oesophageal carcinoma	15	Died 55 months later of another disease.	5,800 r/ 39 days	—
Stevenson and Eckhardt (1945).	1	43	M	Nasopharyngeal lympho-epithelioma (secondaries in cervical nodes).	22	Fatal in 4 months	6,000–8,000 r/ 2 courses.	Yes
Greenfield and Stark (1948).	3	24	M	Retroperitoneal lymph nodes (testicular primaries).	3½	Stationary after 12 months	6,318 r/43 days	—
		20	M		5	,, ,, 18 ,,	4,750 r/89 days	
		28	M		4	,, ,, 17 ,,	4,454 r/83 days	
Boden (1948)	10	73	M	Pharyngeal carcinoma	11	Fatal in 1 month	2,000 r/1 day	Yes
		58	M	,, ,,	4	Died of primary	2,225 r/1 day	—
		56	F	,, ,,	10	Fatal in 4 months	5,200 r/17 days	Yes
		52	F	Lymphosarcoma of neck	12	Stationary after 46 months	3,936 r/17 days	—
		39	M	Cervical Hodgkin's disease	15	Fatal in 4 months	4,210 r/17 days	—
		23	F	,, ,, ,,	11	Fatal in 11 months	4,320 r/17 days	—
		44	F	Pharyngeal carcinoma	5	Transient	5,060 r/17 days	—
		26	M	Cervical Hodgkin's disease	3	Transient	3,000 r/17 days	—
		49	M	,, ,, ,,	6	Transient	3,250 r/17 days	—
		46	F	Lymphosarcoma of neck	1	Transient	3,200 r/17 days	—
Boden (1950)	3	47	M	Laryngeal carcinoma	70	Stationary after 14 months	4,900 r/32 days	—
		48	F	Thyroid carcinoma	13	,, ,, 17 ,,	3,500 r/17 days	—
		54	F	Nasopharyngeal carcinoma	12	Transient	3,000 r/17 days	—
Jacobsson (1951)	13	Not stated		Hypopharyngeal carcinoma	Not stated	5 fatal within 15 months 1 ,, ,, 48 ,, ? others surviving (treated 1939-42)	Not stated	—
Malamud *et al.* (1954)	1	22	M	Nasopharyngeal carcinoma (secondaries in cervical nodes).	10	Fatal in 4 months	5,000 r/20 days	Yes
Itabashi *et al.* (1957)	2	72	M	Lingual lympho-epithelioma (secondaries in cervical nodes).	15	Fatal in 10 months	10,484 air r/ 27 days.	Yes
		41	F	Laryngeal carcinoma	4½	Stationary after 39 months	8,000 air r/ 38 days.	—

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reached a static phase (the period of follow-up varying from twelve to forty-eight months). In a further 5 patients the neurological disorder appears to have been a transient one, the patients being reported as symptom-free at the end of the period of observation. There is no information as to the outcome of the disease in the remaining 7 patients. It will be seen that the prognosis, although serious, is not invariably hopeless. In Boden's (1948) cases the outlook was better in cases with a short latent period between irradiation and the onset of neurological symptoms.

Diagnosis

The diagnosis of radiation myelopathy cannot be based on any particular clinical feature. All elements in the cord may be affected in varying degrees and in various combinations. It cannot be based either on any specific finding obtained in the course of ancillary investigations. The diagnosis depends upon the development of a focal neurological lesion within spinal cord segments submitted to large doses of radiation and upon the exclusion of other causes of myelopathy, particularly spinal compression.

When a patient with treated carcinoma develops an acute paraplegia, spinal compression must first be excluded. Myelography may reveal a metastasis, even if the plain radiographs show no obvious collapsed vertebra. A diagnosis of radiation myelopathy in such a patient should never be considered, in our opinion, until a patent subarachnoid space has been demonstrated. Myelography was performed, in only 3 of the cases reported in Table I (Malamud *et al.*, 1954, and Itabashi *et al.*, 1957).

A chronic paraplegia in a patient with treated carcinoma is unlikely to be due to metastatic spinal compression. In such cases compression from other, unrelated, causes must be excluded by myelography. Subacute combined degeneration of the spinal cord is usually recognized clinically. In doubtful cases a blood or marrow examination and an estimation of serum B_{12} will settle the question. A normal C.S.F. rules out an active syphilitic meningomyelitis. The main differential diagnosis will be from the late "spinal" forms of disseminated sclerosis.

Certain predominantly spinal forms of carcinomatous neuromyopathy may show a superficial resemblance to radiation myelopathy. Brain and Henson (1958) in a detailed review of carcinomatous neuromyopathy admit that "exceptionally, the neuromyopathy may arise after the successful removal of the cancer" but in none of their patients were the lesions obviously focal. Even their "mixed forms," in which posterior column and pyramidal tract degeneration were prominent features, showed concomitant cerebellar signs and were frequently associated with cranial nerve palsies. The evolution in this group was towards severe or complete disability, often within a few months, at the most within two years. This is unlike the relatively benign course seen in some of our cases.

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Pathology

There is some doubt as to the pathogenesis of neural injury following irradiation. Opinions differ as to whether the effect is primarily on nerve cells and their axons or whether the brunt of the damage falls on the connective tissue and blood vessels, a slow endothelial proliferation eventually resulting in ischæmic damage to the parenchyma. Most of the experimental work has been based on animals submitted to large doses of radiation administered over short periods. In such cases the effect on neurons is often the most obvious (a true "radionecrosis") although astrocytic degeneration and blood vessel changes may be quite severe. It is doubtful, however, whether in competent radiotherapeutic practice such necrotizing doses are ever administered.

Very few cases of radiation myelopathy in man have been adequately documented from a pathological point of view (*vide* Table I). Our case reports unfortunately leave this lacuna unfilled. In most instances the blood vessels and stroma appear to have been predominantly involved. In the patient reported by Malamud *et al.* (1954), however, there was "widespread disintegration of the parenchyma," the vascular changes being "distinctly limited in extent."

The latent period of several months between irradiation and the onset of myelopathic symptoms suggests that the effect is primarily one on blood vessels. As Lampe (1958) points out, the changes are "comparable to the late sequelæ of radionecrosis seen at other sites . . . which are known to be due to vasculo-connective tissue damage." The limited pathological findings in our second case would support this contention.

Clinical Material

We here describe 5 further cases of radiation myelopathy. The cases were treated at the Radium Beam Research Unit, the Radiotherapeutic Research Unit of the Medical Research Council, and the Radiotherapy Department of Hammersmith Hospital between 1936 and 1959.

We have used the following criteria for making a diagnosis of radiation myelopathy:

(*a*) that the spinal cord should have been included in the area irradiated.

(*b*) that the main neurological lesion should be within the segments of cord exposed to radiation.

(*c*) that myelography (or necropsy) should have excluded cord compression from metastases as the cause of the neurological disorder.

Four patients who developed neurological signs several months after irradiation were not accepted as cases of radiation myelopathy because of insufficient data. They failed, in particular, to satisfy our third diagnostic criterion.

Case Reports

Case 1.—*Mrs. L. C., aged* 51. *Post-cricoid carcinoma*

This patient was treated in May 1936 by means of a 5-gramme radium beam unit, using 2 anterior and 4 posterior fields extending from the suprasternal notch to the hyoid bone anteriorly, and centred over the seventh cervical spine posteriorly. A maximum tumour dose of 8,700 rœntgens was delivered in thirty-five days. The dose received by the irradiated segments of the spinal cord has been estimated to have been from 5,630 r to 8,700 r. The differential bone absorption of radium gamma radiation is small, but has been taken into account in estimating the cord dose (*vide* Appendix).

The primary cancer regressed completely. Fourteen months after treatment she developed a numb, burning feeling in the left leg which gradually spread to the lower trunk. One month later she was found to have a mild spastic paraplegia with signs predominating on the right. There were no abnormalities in the upper limbs. The abdominal reflexes were absent. Pain and thermal sensation were impaired below the eighth dorsal dermatome on the left. Vibration and postural sensations were intact. Over the next two years her disability progressed very slowly. The level of sensory loss ascended to the sixth dorsal dermatome on the left and the right upper limb reflexes became abnormally brisk.

In 1950, fourteen years after irradiation, her post-cricoid cancer had not recurred. She was still ambulant although her spastic paraplegia had slightly progressed. She had developed some urgency of micturition. The neurological signs were largely unchanged except that the sensory level to pin-prick had now ascended to D5 and that postural and vibration sense were now impaired in the right leg. Investigations, including radiography of the cervical and dorsal spine, W.R. and Kahn, examination of the C.S.F. and myelography, were all normal.

Her condition remained stationary. One day, four years later, she suddenly developed severe lower cervical pain and weakness of both arms. She was readmitted to hospital.

Examination revealed gross diffuse weakness of the upper limbs, predominantly on the right, where only finger movements were possible. There was no atrophy. The arm reflexes were symmetrically sluggish. There was severe spastic weakness of the lower limbs and bilateral hypalgesia over the legs and lower trunk. Pain sense was not impaired in the upper limbs. Vibration sense was grossly impaired over the hands, trunk and lower limbs. Radiographs of the cervical spine were normal. The C.S.F. was normal and there was no manometric block.

Power in the upper limbs improved slightly over the following weeks, but she died a few months later from a myocardial infarction.

Necropsy revealed occlusion of the anterior descending branch of the left coronary artery. There was no evidence of local recurrence or of visceral metastases. The brain appeared normal. No metastases were found in the cervical or dorsal vertebræ. There were no deposits in relation to the spinal meninges. The cord was unfortunately not examined histologically.

Comment.—The development of a Brown-Séquard syndrome suggested that her paraplegia was of spinal origin. The detection, at an early stage, of pathologically brisk reflexes in the right upper limb allowed the lesion to be localized to the upper cervical segments (i.e. to the area irradiated). A myelogram, performed thirteen years after the onset of symptoms, excluded spinal compression. Radiation myelopathy seems the most likely diagnosis.

This case illustrates the extremely slow progression of the disorder in some patients.

Case 2.—*Mrs. K. P., aged* 47. *Carcinoma of left pyriform fossa*

In January 1937 this patient was treated by means of a 5-gramme radium beam unit, using 2 anterior and 4 posterior fields arranged as for Case 1. A maximum tumour

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cord segments being estimated to vary from 4,750 r to 7,000 r. The differential dose of 7,000 roentgens was given in thirty-two days, the dose received by the irradiated absorption in bone has again been taken into account.

The primary tumour regressed, but six months after her treatment was completed the patient developed paræsthesiæ in the left hand, tingling in the feet, progressive weakness of the lower limbs, and eventually retention of urine and fæces. Examination nine months after treatment revealed a right Horner's syndrome, marked spastic weakness in the lower limbs with exaggerated tendon reflexes, extensor plantar responses and impairment of joint position and vibration sense in the legs. There were no abnormal signs in the upper limbs.

Investigations, including W.R. and radiography of the cervical and dorsal spine, failed to demonstrate any abnormality. The C.S.F. was normal and there was no block.

She was thought to have an intraspinal metastasis, although the radiotherapist concerned had pointed out the possibility of radiation damage to the cord.

She was given a further course of radiotherapy to the upper dorsal region at another hospital, an estimated dose of 5,280 r being given in fourteen days. Her condition deteriorated and she died of bronchopneumonia a month later, eleven months after the commencement of the original treatment.

At post-mortem examination there was no evidence of local recurrence or of visceral, spinal or meningeal metastastes. The necropsy report states, however, that "the upper dorsal segments of the cord were atrophic over an area of 4 in., in the same region as the X-ray reaction." Histological examination of the cord revealed no intramedullary metastases, but there was "a vascular lesion which had all the appearance of an infarct."

Comment.—This case illustrates well the dangers of irradiating the cord for presumed metastases without adequate proof, and in particular of treating segments of the spinal cord which have been previously irradiated. The dose given on the second occasion (i.e. 5,280 r in fourteen days) is high when compared with modern practice. The use of posterior fields for the treatment of cancer of the throat, which was common at that time, was discontinued in this hospital following the post-mortem examination of this patient.

Case 3.—*Mr. J. H., aged* 46. *Carcinoma of the left main bronchus*

In November 1954 this patient received a course of supervoltage radiotherapy. He was given a mean tumour dose of 4,410 rads in twenty-eight days by means of the 8 MeV linear accelerator, using two opposed fields centred to the left of the mid-line at the level of the sixth dorsal spine. The estimated dose received by spinal cord segments D3–D7 was 4,410 rads, allowance being made for the small differential bone absorption of 8 MeV X-rays. The response of the primary was excellent and to date the patient has shown no sign of recurrence.

Seven months after his irradiation he complained of tingling in both lower limbs. One month later he began dragging his right leg and shortly afterwards complained that his left leg also felt heavy.

Examination fourteen months after treatment showed signs of extensive fibrosis of the left lung. The cranial nerves and upper limbs were normal (a recurrent laryngeal palsy present previously had cleared completely). The lower limbs were weak and spastic. There was clonus at both knees and ankles and the plantar responses were extensor. The abdominal reflexes were absent. Superficial sensation was intact but vibration sense was depressed below the level of the iliac crests. Postural sense was impaired in the toes.

Radiographs failed to reveal any metastases in the spine (fig. 1, Plate XLIX), but

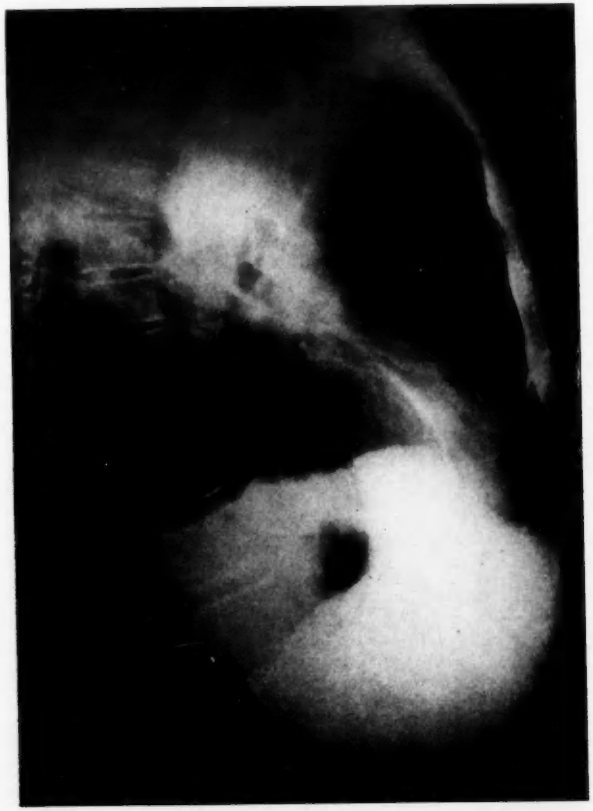

FIG. 1.

FIG. 2.

To illustrate article by Christopher A. Pallis, Sydney Louis and Rowland L. Morgan.

confirmed the fibrosis of the left upper lobe. There was no serological evidence of syphilis and the alkaline phosphatase was normal. No evidence of cord compression was found at lumbar puncture or myelography.

Over the next forty months his chest condition remained stationary. There was no evidence either clinically or radiologically of any recurrence or metastases from his bronchial tumour. He had, however, complained of occasional flexor spasms in his legs and difficulty in initiating micturition.

Radiography fifty-two months after treatment revealed partial wedging of the upper eight dorsal vertebræ, these changes being most obvious in D5, D6, D7 and D8 (fig. 2). The bone pattern was not altered and there was no erosion of the cortex. The neurological signs had progressed only slightly. The upper limbs and cranial nerves were normal but the spastic paraplegia had slightly increased. The sensory loss had advanced, vibration sense now being absent up to the costal margins. Postural sense was severely impaired in the toes and ankles and there was tactile loss in both legs. Pain and thermal sensation were unaffected. Radiologically, no evidence of recurrence or metastases could be found. Lumbar puncture and myelography again failed to demonstrate any obstruction.

The patient is still alive six-and-a-half years after the original treatment.

Comment.—Symptoms of a slowly progressive myelopathy appeared within seven months of irradiation. The lesion was within the segments of the cord irradiated. Spinal compression from metastatic disease was excluded (*a*) because the myelopathy progressed only slightly over a period of five-and-a-half years, and (*b*) because of the repeated normality of the C.S.F., of the manometric response to jugular compression, and of the myelograms. Radiation myelopathy is the most probable diagnosis.

The late appearance of radiological changes in several vertebræ (all within the irradiated field) was not considered to invalidate this conclusion. It was felt that the bony changes could not be directly responsible for the myelopathy, in view of the patency of the subarachnoid space on myelography. It was thought more likely that both bony changes and myelopathy were radiation effects. It is well known that there may be a latent period of many months before radionecrosis of bone becomes radiologically apparent. The subsequent evolution of the osseous lesion is in keeping with this suggestion.

Case 4.—*Mrs R. F., aged* 50. *Post-cricoid carcinoma*

In May 1955 this patient was treated by supervoltage radiation and given a total tumour dose of 5,830 rads in forty-two days by means of one anterior and two postero-lateral fields. The spinal cord in the region of the third, fourth and fifth cervical vertebræ received a dose estimated at 4,600 rads. The tumour rapidly disappeared.

Eighteen months later her left leg became stiff, her gait awkward, and she developed attacks of spontaneous clonus of the left foot. She also complained of weakness of the left arm and experienced occasional paræsthesiæ in both calves and groins. Her sphincter control was not impaired.

On examination there was diffuse atrophy and weakness of the left upper limb, which was slightly spastic. No fasciculation was seen. Power was normal in the right arm. Both legs were weak and spastic. The tendon reflexes were pathologically brisk in all four limbs, particularly on the left. The plantar responses were both extensor. Pain and thermal sense were impaired over the left little finger, over the medial border of the left forearm, and in the whole of the right lower limb up to groin level. Other modalities of sensation were normally perceived.

Radiographs of the cervical spine showed no abnormality. The C.S.F. was normal. There was no manometric block. A myelogram showed a very small indentation

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opposite the C6–C7 disc. The findings were not thought sufficient to account for her gross symptoms and signs. Hæmatological and serological investigations excluded pernicious anæmia and syphilis.

Her weakness progressed, her gait deteriorated, and she was admitted to another hospital twenty-three months after irradiation, having fallen and sustained a fractured left femur. Examination revealed a spastic tetraplegia, more severe on the left. All modalities of sensation were impaired below the fifth cervical segment. Radiographs of the cervical spine again failed to demonstrate any metastases. She remained bedridden and died of bronchopneumonia twenty-six months after her course of radiotherapy.

Post-mortem examination revealed no evidence of local recurrence or of visceral, vertebral or meningeal metastases, but unfortunately histological examination of the spinal cord was not performed.

Comment.—In this case there was myelographic evidence of mild cervical spondylosis. Extensive bilateral sensory loss of the type shown by this patient is most unusual in this condition. Radiation damage seems a more probable cause of her myelopathy.

This case differs from the others in that there was a lower motor neurone disturbance in the left arm in addition to the more usual involvement of the long ascending and descending tracts.

Case 5.—Mrs C. B., aged 52. Carcinoma of the thyroid with involvement of cervical nodes

In February and March 1959 this patient was treated by conventional 240 kV radiotherapy. The irradiated area included both the thyroid and the mass of glands, a total tumour dose of 4,200 r being given in thirty-nine days through two lateral fields. The dose received by the subjacent spinal cord segments was estimated to be between 1,150 r and 3,680 r. The lowest segments irradiated were probably the first and second dorsal. The mass of glands and the thyroid nodule regressed considerably but did not disappear completely. Three months after irradiation, a total thyroidectomy and excision of the residual glandular mass was performed. For technical reasons a small remnant of malignant tissue, firmly attached to the left side of the trachea, could not be resected.

A further course of radiotherapy was therefore administered four months after the original course. A total tumour dose of 5,050 rads in twenty-seven days was given on the 8 MeV linear accelerator. Super-voltage radiation was used in order to reduce the radiation dose to the skin and normal tissues. The upper two dorsal segments of the cord were unavoidably irradiated by the penumbra of the beam, and it is estimated that these segments received 1,700 rads. These two segments were therefore irradiated during both courses of radiotherapy.

The patient remained well until October 1959, four months after the second course. She then noticed numbness of the left leg below the knee, associated with loss of thermal sense. Two weeks later similar symptoms were noticed on the right. Her legs felt stiff and awkward and she had difficulty in assessing their position. These symptoms gradually progressed.

Two months later she developed a sudden severe pain between the scapulæ, radiating round the upper thorax. This quickly subsided but was followed by rapid progression of her motor disability. Flexor spasms developed and her walking deteriorated markedly. The numbness gradually spread up on to the abdomen and thorax. In early January 1960 she developed acute retention of urine.

Examination revealed no evidence of local recurrence and no tenderness over the spinous processes. Power and sensation were normal in the upper limbs, but the arm

reflexes were extremely brisk on both sides. The lower limbs showed a total spastic paralysis with clonus at knees and ankles and bilateral extensor plantar responses. All modalities of sensation were severely impaired below the third dorsal dermatome on the right and the fifth dorsal dermatome on the left.

Radiography of the chest, cervical and dorsal spine, pelvis and skull was normal. There was no evidence of syphilis or pernicious anæmia. The C.S.F. was normal and a myelogram revealed no obstruction. There were, however, small indentations opposite disc spaces C4–C5, C5–C6, and C6–C7. It was thought unlikely that these were contributing to her very severe and fairly acute myelopathy because the cervical canal appeared capacious. Myelography was repeated on two further occasions, the last being ten months after the development of her paraplegia, and no obstruction has been demonstrated. Her condition has remained stationary. Her tumour has not recurred thirty months after the original treatment.

Comment.—An extramedullary metastasis is unlikely in view of the normal radiological appearances of the vertebræ, the repeated absence of myelographic obstruction, and the repeatedly normal C.S.F. findings. An intramedullary metastasis has not been entirely excluded. The myelograms were normal, however, in the presence of an extremely severe neurological disorder amounting to a total transection of the cord. There was no evidence of metastatic disease elsewhere and the patient's general condition remains satisfactory.

It would be an extraordinary coincidence for an intramedullary metastasis, itself a rare lesion, to occur in precisely those segments of the spinal cord which received irradiation during both courses of treatment. Radiation myelopathy seems the most likely diagnosis.

The main facts relating to the above 5 cases are summarized in Table II.

TABLE II

	Age	*Sex*	*Lesion irradiated*	*Latent period (months)*	*Prognosis*	*Estimated cord dose*
Case 1	51	F	Post-cricoid carcinoma	15	Slow progression over 17 years	5,630–8,700 r in 35 days
Case 2	47	F	Pharyngeal carcinoma	7	Fatal in 4 months	4,750–7,000 r in 32 days
Case 3	46	M	Bronchial carcinoma	7	Slow progression over 66 months	4,410 rads in 28 days
Case 4	50	F	Post-cricoid carcinoma	18	Fatal in 8 months	4,600 rads in 42 days
Case 5	52	F	Thyroid carcinoma (cervical secondaries)	8	Severe paraplegia within 3 months	1,150–3,680 r in 39 days and 1,700 rads in 27 days

DISCUSSION

(*a*) *Radiation Tolerance of the Spinal Cord*

The sensitivity of the spinal cord to damage by irradiation has now been estimated in a number of animal experiments (Pendergrass *et al.*, 1922; Cairns and Fulton, 1930; Peyton, 1934; Davidoff *et al.*, 1938; McLaurin *et al.*, 1955). The conditions of these experiments, however, bear little resemblance to those encountered in clinical practice. Most of the reports

deal with the effects of high dose irradiation, administered over short periods.

The radiation tolerance of the adult human cord is difficult to estimate with any accuracy. The volume of tissue irradiated, the overall duration of irradiation, and the total dose administered must all be taken into account. As vascular damage is probably an important factor in determining the biological effects of irradiation, such variables as the number of blood vessels and their effective diameters may play a role in determining individual susceptibility.

Boden (1948, 1950) suggested that the dose to the spinal cord should not exceed 3,500 r in seventeen days with large field techniques, and 4,500 r in seventeen days for small fields. He made it clear that these doses were estimated without regard to bone absorption. These doses are biologically equivalent to 3,650–4,700 r in twenty-one days, 3,900–5,000 r in twenty-eight days, and 4,300–5,500 r in forty-two days (Strandqvist, 1944) or, expressed in rads, to 3,500–4,500, 3,700–4,800, and 4,100–5,200 rads in twenty-one, twenty-eight and forty-two days respectively. Lampe (1958) agrees by implication with Boden's suggested limits, but emphasizes the inaccuracy of some of the doses reported in the literature. Many were estimates made in retrospect, using depth-dose tables with no allowance for bone absorption.

It has long been recognized that the roentgen is an unsatisfactory unit when considering the biological effects of radiation. In the last decade a basic energy unit, the rad (equal to 100 ergs per gramme of tissue) has been used as the unit of absorbed dose. In so far as the energy per roentgen absorbed by any tissue depends upon the type of radiation (in particular its half value layer), it is logical to use the rad rather than the roentgen as a basis for comparing doses of radiation producing specific biological effects.

The accounts of 21 previously reported cases of radiation myelopathy contain details of dose and of the overall duration of treatment. Sufficient information is available in these reports (and in our present series of 5 cases) to enable the dose received by the cord, in each instance, to be estimated in rads. This facilitates comparison despite the varying types of radiation used. In 2 cases out of this total of 26 (our Case 5 and the case of Stevenson and Eckhardt, 1945) the patient received two courses of treatment separated by several months. In view of the doubt as to whether it is valid to summate doses when courses of treatment are separated by long intervals, these 2 cases have been excluded from our proposed comparison. The information available for the remaining 24 cases has been used to calculate the dose received by the cord in rads after making the appropriate correction for bone absorption (*vide* Appendix).

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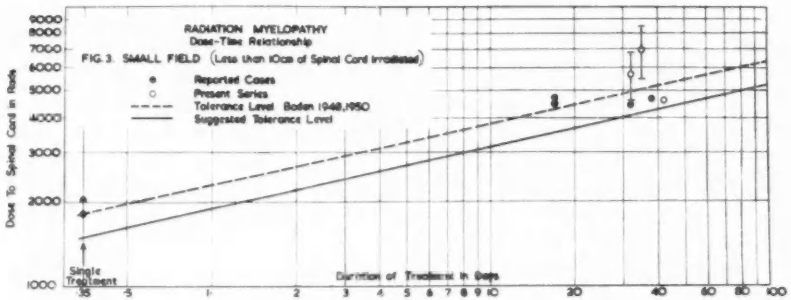
TABLE III—CORD DOSES (IN RADS) IN 24 ADEQUATELY DOCUMENTED CASES OF RADIATION MYELOPATHY

Case		*Radiation used*	*Reported dose to cord*	*Conversion factor roentgens to rads*	*Estimated dose to cord in rads corrected for bone absorption*	*Duration of treatment in days*
SMALL FIELDS						
Boden (1948)	Case 1		2,000 r	0·95	1,800	Single
	2	Details not given but H.V.L.	2.250 r	0·95	2,040	Single
	3	assumed to be 2–3 mm. copper	5,200 r	0·95	4,690	**17**
	7		5,060 r	0·95	4,560	**17**
Boden (1950)	Case 1		4,900 r	0·95	4,420	**32**
Itabashi (1957)	Case 2	250 kVp X-rays: H.V.L. 2–3 mm. copper	8,000 air roentgens	0·95	4,650	**38**
Present series	Case 1	Radium gamma	5,630–8,700 r	0·97	5,460–8,440	**35**
	2	Radium gamma	4,750–7,000 r	0·97	4,600–6,780	**32**
	4	8 MeV X-rays	4,600 rads	1·0	4,600	**42**
LARGE FIELDS						
Smithers (1943)		400 kVp X-rays: H.V.L. 3·7 mm. copper	5,800 r	0·965	5,550	**39**
Greenfield & Stark (1948)	Case 1	1 MeV X-rays:	6,318–6,480 r	0·966	6,100–6,260	**44**
	2	H.V.L. 3·6 mm. lead	4,750–5,400 r	0·966	4,580–5,210	**90**
	3		4,454–5,488 r	0·966	4,300–5,300	**84**
Boden (1948)	Case 4		3,936 r	0·95	3,550	**17**
	5		4,210 r	0·95	3,800	**17**
	6		4,320 r	0·95	3,900	**17**
	8	Detail not given but H.V.L.	3,000 r	0·95	2,710	**17**
	9	assumed to be 2–3 mm. copper	3,250 r	0·95	2,860	**17**
	10		3,200 r	0·95	2,850	**17**
Boden (1950)	Case 2		3,500 r	0·95	3,160	**17**
	3		3,000 r	0·95	2,710	**17**
Malamud *et al.* (1954)		250 kVp X-rays: H.V.L. 1·37 mm. copper	5,000 r	0·95	4,520	**20**
Itabashi (1957)	Case 1	250 kVp X-rays: H.V.L. 3 mm. copper	10,484 air roentgens	0·95	6,140	**27**
Present series	Case 3	8 MeV X-rays	4,410 rads	1·0	4,410	**28**

FIG. 3.



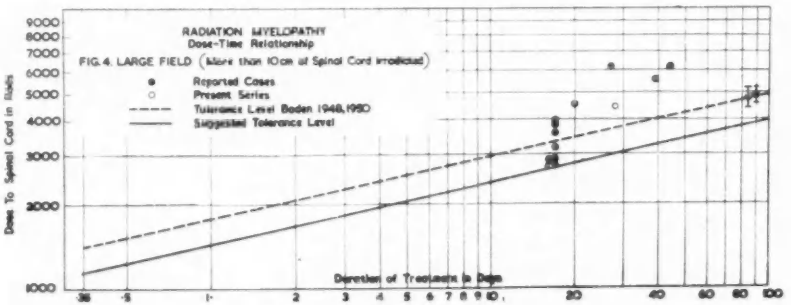

RADIATION MYELOPATHY
Dose-Time Relationship
FIG. 4. LARGE FIELD (More than 10cm of Spinal Cord Irradiated)
Reported Cases
Present Series
Tolerance Level Boden 1948,1950
Suggested Tolerance Level
Dose To Spinal Cord in Rads
Duration of Treatment in Days

FIG. 4.

Table III shows the results of these calculations. Figs. 3 and 4 show the dose in rads received in these 24 cases plotted against the overall duration of treatment. Fig. 3 relates to those cases where the length of cord irradiated appeared to be less than 10 cm., and fig. 4 to those cases where the length irradiated was greater than 10 cm. On each graph we have drawn a dotted line representing Boden's suggested limits for radiation dose to the spinal cord. (These doses have also been converted to rads.) It would appear from the graphs that cases of myelopathy have developed after the cord had received doses smaller than those suggested by Boden. In 3 cases where a small field technique was used and in 5 cases of large field irradiation the cord dose was less than that suggested by Boden as safe.

There is therefore some justification for suggesting that doses of radiation hitherto accepted as safe may well be too high. We shall return to this point later.

(*b*) *Incidence of Myelopathy*

The incidence of radiation myelopathy is difficult to assess. Ahlbom (1941) reported 4 cases out of 235 patients irradiated, an incidence of 1·7 per cent. Greenfield and Stark (1948) reported a similar figure (3 out

of 180 patients irradiated). Jacobsson (1951) gives a much higher incidence. 13 of his 157 patients (8·3 per cent) developed myelopathy.

These data are not very helpful, however. In some instances the doses received by the spinal cord were not mentioned. In others doses are mentioned for the patients who developed myelopathy, but not for the other cases irradiated. Such statements leave the crucial questions unanswered. How often are cord doses administered, as large as those delivered to patients subsequently developing myelopathy, *without* neurological complications ensuing? In other words, is the development of radiation myelopathy a question of idiosyncrasy or is it solely related to the dose received by the cord? Or does idiosyncrasy play a role, but only above a certain dosage level? And if so, what is this level and how important is this role?

Boden (1948, 1950) first attempted to answer these questions. He related the development of myelopathy both to the dose delivered and to the volume of tissue irradiated. He showed for instance that with cord doses of less than 3,500 r in seventeen days the incidence of myelopathy was 3 per cent (the neurological disturbance in all these cases being reversible), whereas with doses greater than 3,500 r in seventeen days the incidence rose to 23 per cent (the neurological disorder proving irreversible). He reported a much higher incidence with small field (25 per cent) than with large field techniques (4 per cent).

We have attempted to carry this analysis a little further. In spite of the difficulties previously mentioned, we have tried to give some indication of the incidence of myelopathy in two specific groups of patients in all of whom it was known that the cord had been irradiated and in whom it was possible to estimate the cord doses administered in every case.

Between 1953 and 1958, 124 patients with large carcinomata of the bronchus necessitating wide field irradiation were treated radically on the 8 MeV linear accelerator. Treatment in each of these cases involved irradiation of more than 10 cm. of the spinal cord. The isodose distribution in each case was calculated before treatment was begun.

Of this group of 124 patients, 53 survived one year and 18 survived two years. 37 patients received spinal cord doses of 4,000–4,500 rads in twenty-eight days, and 16 a dose of 3,000–3,500 rads in twenty-eight days. Of the 37 one-year survivors who had received the higher dose, only one (our Case 3) developed myelopathy. No cases of myelopathy were encountered among patients who had received the smaller dose. No further cases of myelopathy occurred during the second year of survival.

The figures relating to post-cricoid carcinoma are a little more difficult to analyse. Between 1936 and 1958, 110 patients with post-cricoid carcinoma were treated (39 by a radium beam unit, 49 by 200–240 kV X-rays, and 22 on the 8 MeV linear accelerator). In each case, less than 10 cm. of the spinal cord was irradiated.

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Of the 39 patients treated by radium gamma radiation, 13 survived one year and 9 survived two years. The doses received by the spinal cord in these cases were all in excess of 4,600 rads in forty-two days. 2 cases of myelopathy were observed in this group (our Cases 1 and 2). These occurred during the second and first years after treatment respectively.

Of the 49 patients treated by 200–240 kV X-rays, 10 survived one year and 6 survived two years. The doses received by the spinal cord varied from 4,000–5,000 rads in forty-two days. No case of radiation myelopathy was observed in this group.

Of the 22 patients treated on the 8 MeV linear accelerator 7 survived one year and 1 survived two years. Five of these patients received cord doses of less than 4,300 rads in forty-two days. No case of radiation myelopathy was observed in this sub-group. Two patients received larger doses. One received 4,600 rads in forty-two days and developed myelopathy in the second year (our Case 4). The other patient received between 4,500 and 5,000 rads in forty-two days and, although surviving fourteen months, did not develop myelopathy.

It will be seen that in patients where large areas of the spinal cord are irradiated (our cases of bronchial carcinoma), no case of radiation myelopathy was encountered among 16 one-year survivors having received cord doses of less than 3,500 rads in twenty-eight days. One case of myelopathy was seen among 37 one-year survivors having received over 4,000 rads in twenty-eight days.

In patients where small areas of the cord were irradiated (our case of post-cricoid carcinoma), no case of radiation myelopathy was seen among 5 one-year survivors who had received doses of less than 4,300 rads in forty-two days. Two cases of myelopathy were seen among 25 one-year survivors having received doses of over 4,300 rads in forty-two days (the vast majority of these patients had in fact received over 4,500 rads in forty-two days).

It would appear that with large field techniques the risk of myelopathy is negligible with cord doses below 3,500 rads in twenty-eight days. With larger doses myelopathy becomes a risk. In our series of patients with bronchial carcinoma its incidence at dose levels above 4,000 rads in twenty-eight days was 1 in 37 (2·7 per cent).

With small field techniques, the risk of myelopathy is negligible with cord doses of less than 4,300 rads in forty-two days. With larger doses myelopathy becomes a risk. In our series of patients with post-cricoid carcinoma its incidence at dose levels above 4,300 rads in forty-two days was 2 in 25 (8 per cent).

(*c*) *Conclusion*

Having considered both the radiation dose received by the spinal cord in patients developing myelopathy and the incidence of myelopathy in

TABLE IV—RADIATION TOLERANCE OF THE SPINAL CORD

	Single dose	17 *days*	21 *days*	28 *days*	35 *days*	42 *days*
Boden (1950) in roentgens	1,490–1,920*	3,500–4,500	3,650–4,700	3,900–5,000	4,100–5,300	4,300–5,500
Conversion to rads (assuming 0·95 rads per roentgen)	1,420–1,820	3,330–4,275	3,470–4,460	3,710–4,760	3,890–5,000	4,090–5,225
Suggested tolerance in rads	1,150–1,490	2,700–3,500	2,800–3,700	3,000–3,950	3,170–4,100	3,300–4,300

*The lesser values apply to cases where more than 10 cm. of cord is included in the irradiated field. The higher values apply when less than 10 cm. have been irradiated.

patients receiving known doses of radiation, we have come to the conclusion that new limits should be advised for the permissible dose of radiation to the spinal cord.

Our proposed new limits are shown by the unbroken lines in figs. 3 and 4. For treatment times of forty-two days the limit for fields greater than 10 cm. long should be 3,300 rads, and for fields less than 10 cm. long, 4,300 rads. The unbroken lines (and Table IV) show what the corresponding doses would be for treatment times other than forty-two days. It will be seen that our proposed limits are some 20 per cent lower than those of Boden.

Idiosyncrasy is obviously a factor in the development of myelopathy. Our survey shows that many patients fail to develop the condition despite having received doses above 3,000 rads in twenty-eight days (for large fields) or 4,300 rads in forty-two days (for small fields).

Whatever the precise limits which may be determined by further observation, it is important to recognize the relative sensitivity of the spinal cord to irradiation, and to plan treatment accordingly. With conventional 240 kV machines (and with some cobalt units) the radiation beam has a wide penumbra. This sometimes makes it difficult to avoid irradiating the cord (for example in post-cricoid cancer, where the irradiated volume must include the anterior surface of the cervical vertebræ). Supervoltage machines however, such as the linear accelerator, produce a very much better collimated beam with little penumbra. With such machines it is usually much easier to avoid irradiating the cord.

With supervoltage radiation the energy absorbed in bone is very nearly equal to that absorbed in soft tissue. The dose delivered to the spinal cord can therefore be estimated more accurately than with lower energy radiation. In view of this, supervoltage radiation is probably the method of choice in the treatment of tumours adjacent to the spinal cord.

Radiation myelopathy is clearly an important hazard in radiotherapeutic practice. Patients submitted to irradiation likely to affect the spinal cord are suffering from malignant disease which may carry a bad prognosis. The dilemma confronting the radiotherapist is whether to administer a sufficient tumour dose, at times unavoidably exposing the cord to dangerously high doses, or whether to avoid the cord at the risk of reducing the tumour dose to below effective levels. To some extent, therefore, irradiation of the spinal cord must always be a calculated risk.

Summary

Thirty-eight previously reported cases of radiation myelopathy are reviewed with regard to early symptoms and signs, differential diagnosis, prognosis, nature of the primary lesion irradiated, and latency between irradiation and the development of neurological symptoms.

A further 5 cases are described, including one in whom a hitherto un-

recorded feature was observed, namely the association of myelopathy with radionecrosis of the overlying bone.

The pathological basis of radiation myelopathy is briefly reviewed.

The difficulties in estimating the radiation tolerance of the human spinal cord are discussed and some facts are presented in relation to the incidence of radiation myelopathy in patients with irradiated bronchial and post-cricoid carcinoma.

On the basis of a review of all previously reported cases and of our own material, new limits are proposed for the dose of radiation which may safely be tolerated by the human spinal cord.

Acknowledgments

We acknowledge with gratitude the advice and help given us by Dr. C. A. P. Wood, Director of the M.R.C. Radiotherapeutic Research Unit, and by Dr. R. Morrison and Dr. T. J. Deeley of the Radiotherapy Department, Hammersmith Hospital. We wish to thank Dr. J. St. C. Elkington for permission to report Case 1.

APPENDIX

In each case of radiation myelopathy where sufficient data were available the dose received by the spinal cord has been calculated in rads. This has necessitated converting many doses expressed in rœntgens in the original papers. The appropriate conversion factor, in each case, is set out in Table III.

These factors assume a value for W (the energy required to form 1 electron pair) of 34 electron volts. This is in accordance with the latest recommendation of the International Commission on Radiological Units and Measurements.

Certain further explanations relating to the conversions are necessary. Boden (1948, 1950) gives no details of the type of radiation used in the treatment of his patients. For these cases a certain figure must be assumed for the half value layer. The cases were treated between 1942 and 1946. A half value layer of 2·0–3·0 mm. copper might be a reasonable assumption. Itabashi (1957) gives full details of the radiation used but quotes the dose to each of 4 fields in air roentgens, that is, without backscatter. In his first patient each of the 4 fields is stated to have received 2,641 air roentgens and the total dose delivered is quoted as 10,484 air roentgens. This total dose is clearly neither the tissue dose delivered to the tumour not that delivered to the spinal cord. The dose delivered to the cord in this case has been estimated at 6,140 rads after allowing for bone absorption and assuming a patient of average dimensions. In Itabashi's second case the cord dose has been estimated as 4,650 rads.

The energy given to soft tissue in the so-called "bone shadow" is less than that estimated from isodose curves. This is not strictly true, however,

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for soft tissues within 50–100 microns of the bone surface. The soft tissue dose here may be several times greater than that at points situated at more than 100 microns from the interface. In our calculations the dose received by the spinal cord has been taken as similar to that received by soft tissue situated at least 100 microns away from the interface. This is also the dose received by soft tissue structures such as blood vessels surrounded by bone, provided they lie in a cavity at least 200 microns in diameter.

The effect of bone absorption in reducing the dose to the spinal cord depends on the type of radiation used. With radiation of half value layer of 2 mm. copper, the reduction in dose received by the cord in a typical treatment would be about 5 per cent. For radium gamma radiation and X-rays of 1 MeV peak and above, the reduction is negligible.

Our estimates of cord doses received by previous patients with radiation myelopathy are based on the reported physical factors of irradiation. We do not think our calculations err by more than 10 per cent at the most. With regard to doses estimated in our own cases the error is probably less than 5 per cent.

No attempt has been made to allow for the differing relative biological efficiency of the radiations used.

Cases 1 *and* 2: These cases were treated by a radium beam unit in 1936 and 1937. It was not until late in 1937 that the roentgen was recognized internationally as applicable to radium gamma radiation. Before then it was customary to quote doses in terms of milligram-hours.

The dose given to each patient treated with the Radium Beam Unit had been carefully recorded at the time. Sufficient data were available in the records for the dose to be recalculated in roentgens, after this unit had been recognized.

The records included a photograph of the treated area, with the actual field positions marked on the skin together with caliper measurements of the relevant dimensions of the patient.

In order to calculate the dose received by the spinal cord we have used these data on a volunteer, whose dimensions and general shape matched those of Cases 1 and 2 as given by the photographs and records. A horizontal cross section of the subject was drawn on which were superimposed the field positions together with the position of the spinal cord as determined from lateral radiographs. The dose to the cord was then determined from isodose curves, making due allowance for the small differential bone absorption of the radium gamma radiation.

Cases 3 *and* 4: These patients were treated recently. It has been our practice to prepare a complete isodose distribution plan, upon which the tumour and neighbouring structures such as the cord are marked, for each patient treated on the linear accelerator. From this plan the dose to the cord and other vital structures can readily be calculated.

Case 5: This patient was first treated by means of conventional 240 kV

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X-radiation. In view of the relatively wide penumbra obtained with this irradiation the exact dose received by the cord is subject to some uncertainty. The probable dose range, however, has been calculated, taking into account the bone absorption. The second course of radiation was given by means of the 8 MeV linear accelerator and the cord dose has been estimated from the treatment plan as in Cases 3 and 4.

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KLÜVER-BUCY SYNDROME IN MONKEYS WITH NEOCORTICAL ABLATIONS OF TEMPORAL LOBE[1]

BY

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INTRODUCTION

KLÜVER and Bucy's classical article on "Psychic blindness and other symptoms following bilateral temporal lobectomy in rhesus monkeys," which appeared in 1937, has undoubtedly been the stimulus for an unprecedented interest in the neurological basis of behaviour.[4] Among the many problems which have arisen from their original work, two have led to the present investigation: One is concerned with the meaning, and the other with the "differential" localization of the behavioural changes resulting from temporal lobe damage. Klüver himself has recently (1958) reviewed the status of both issues. As regards the question of localization he stated: "Intensive researches along behavioural lines during the last twenty years have not settled the question of the particular anatomical structures related to each of the symptoms."

The present study was originally designed to clarify the nature of the visual abnormalities found in the Klüver-Bucy syndrome by restricting the temporal lobe surgery to the neocortical areas. Meyer (1958) has already reported on the psychological findings, and the present paper represents the anatomical counterpart. As he pointed out, the changes observed in these experimental animals not only included "psychic blindness" but also the release of oral tendencies and the well-known taming effect. Thus, a partial Klüver-Bucy syndrome had developed in spite of the fact that the ablations had been restricted to the neocortical

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[4]Attention was first drawn to the peculiar effects of bilateral temporal lobectomy by Brown and Schäfer as long ago as 1888.

gyri of the temporal lobe. This outcome prompted a thorough histological analysis of the actual brain damage, including secondary changes. The following two questions received special attention: (1) Were the amygdala, hippocampus, entorhinal cortex and other so-called rhinencephalic components of the temporal lobe damaged? (2) Was there secondary degeneration suggesting fibre connexions between temporal neocortex and rhinencephalon? The answers to these questions should provide an explanation of the unexpected behavioural changes which occurred in the animals of this series.

Methods

Nine immature *M. mulatta* monkeys were used (weights varied from 1·9 to 2·6 kg.). The ablations were performed by one of us (C. N. W.) under aseptic conditions and using nembutal anæsthesia. Bilateral temporal bone flaps were turned and the cortical areas, outlined in fig. 1, were removed with suction pipettes. An attempt was made to remove all cortical grey matter subpially to preserve the vascular supply of adjacent tissues. Encroachment upon rhinencephalic structures and auditory areas, as well as auditory and visual radiations was carefully avoided.

The animals underwent psychological testing and training before and after surgery, and were observed in their home cages. The psychological problems used were in discriminative learning and learning set formation (for details *see* Meyer, 1958). The animals were observed for the appearance of symptoms characteristic of the Klüver-Bucy syndrome. Simple testing was begun immediately after operation and continued for one month. After this, the formal testing programme was begun and lasted for a further twenty weeks, and cage observations were continued until the time of sacrifice approximately six to seven months after surgery. The brains were perfused *in vivo* with a 10 per cent formalin solution. Photographs and wax casts of the specimens were made to enhance reconstruction work. All of the brains were paraffin embedded except one which was embedded in celloidin. Alternating sections 30 μ thick, were stained with thionin and mounted. In one case, an additional series consisting of every fifth section was prepared with Weil stain.

The reconstruction of cortical lesions was done with the aid of a set of outline drawings of every 50th section (Edinger apparatus, magnification ×30), to which further details were added with the aid of microscopic studies. From these coronal sections, reconstructions were made by projecting the damaged areas on to photographs of side and basal views of the individual brains.

The rhinencephalon was studied with special care. For this purpose two separate histological analyses were done, one by K. A. and the other by R. G. The results were found to be generally in agreement, and only in a few points was it necessary to re-examine the material before full accord was reached. Normal brains of rhesus monkeys of approximately equal size, and sectioned at a similar plane were used to compare rhinencephalic boundaries, and to determine the extent to which rhinencephalic areas had been preserved or ablated. Photomicrographs of several representative levels of basal temporal cortex were taken and an additional set of projected drawings of important areas along the rhinal fissure was prepared in order to clarify the situation (fig. 4).

Results

I. Behavioural Changes

Post-operatively, at periodic intervals, the animals were tested with an aggregation of inedible and edible objects such as brass nuts, raisins,

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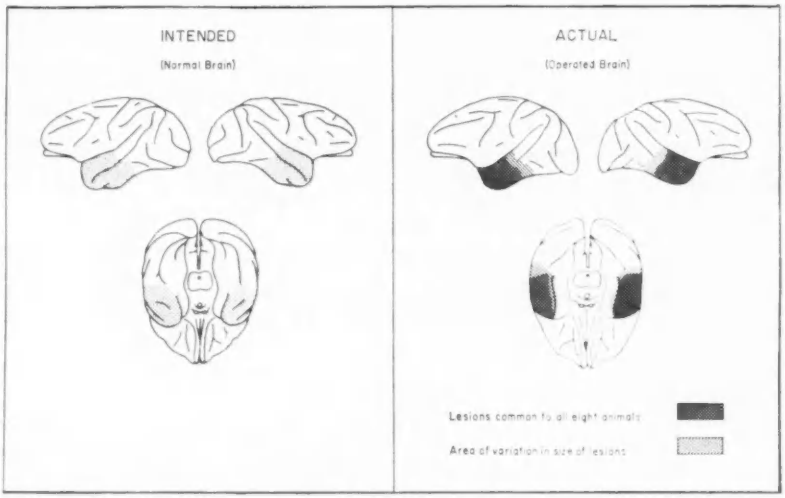

FIG. 1.

peanuts and pellets compressed from staple diet. In this situation, the monkeys from the first showed a preference for the food, but none the less engaged in a pattern of mouthing and then rejecting the inedible objects. This behaviour developed within the first post-operative days; however, it then began to wane, and was present only as a trace when observations were concluded. There was no increase in food intake nor was there any significant weight gain.

A more persistent universal change in reactivity to fear-provoking objects was noted. From the first, the animals showed no fear of brooms or nets or hoses. A toy snake, from which normal monkeys fled screaming, elicited a mouthing exploration by all operated monkeys. After a month of post-operative recovery, this tendency grew less pronounced, but even then all animals would still approach such objects within not more than thirty seconds. The monkeys, throughout their post-operative career, reacted violently only to physical restraint; they would bite if held down firmly, but would do so with substantially less vigour than the normal animals.

In general, the picture is that of the Klüver-Bucy syndrome. It is not complete in the sense that the monkeys (which were juveniles), failed to show the sexual aberrations, and none would eat ground meat, which was proffered to them upon a number of occasions. However, the bold

approach to objects generally, and their exploration with the mouth, proved to be quite prominent.

The acquisition and retention of a general solution for a single visual discrimination problem and a learning set formation were tested in the following manner: Pre-operatively the eight monkeys were divided into two groups. One group was trained in the single visual discrimination problem and the other in the learning set formation. Post-operatively both groups were tested in both problems. This allowed testing for retention of a previously learned problem and for the ability to learn a new one, each group serving as the control for the other. Pre-operatively following training, the single visual habit was performed at a 90 per cent correct response level. Post-operatively in this same group one monkey (242) retained the 90 per cent level. Two others regained the 90 per cent level, after some delay. The fourth monkey (263), which had the most extensive lesions, lost the habit entirely. However, in the group that

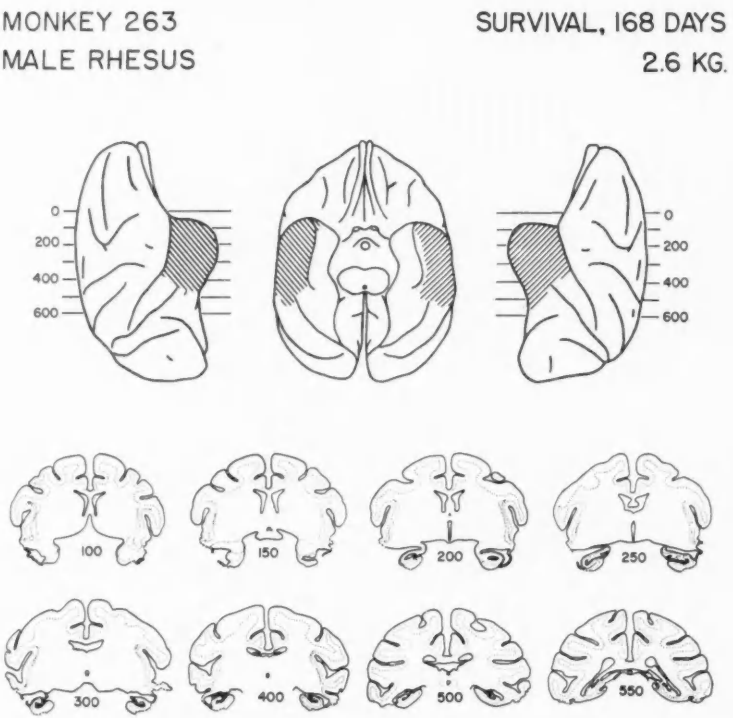

FIG. 2.—Reconstruction of cortical lesion. This case has the most extensive damage of the group.

had no previous training in the single visual problem, only one monkey attained a 70 per cent correct response, post-operatively, and the remaining three reached between 50–60 per cent after twice the time needed to produce a 90 per cent response prior to surgery. It would seem, then, that temporal neocortical ablations have a more profound effect on learning a single visual discrimination problem than on the retention of it.

In the area of learning set formations, the results were essentially the same. Again animal 242 performed better. The most likely explanation for this animal's behaviour is, as mentioned below, that its lesion represents the smallest total neocortical ablation.

II. Extent of Ablations

At the outset it can be said that the lesions, by sparing rhinencephalon and auditory cortex, paralleled the intended boundaries and showed a striking degree of uniformity (fig. 1). Since the latter renders verbal description of individual cases repetitious, a description of a representative case (fig. 2) is given, and the results of all reconstructions are presented in a series of brain charts (fig. 3).

UNIFORM REMOVAL OF TEMPORAL NEOCORTEX IN THE RHESUS MONKEY

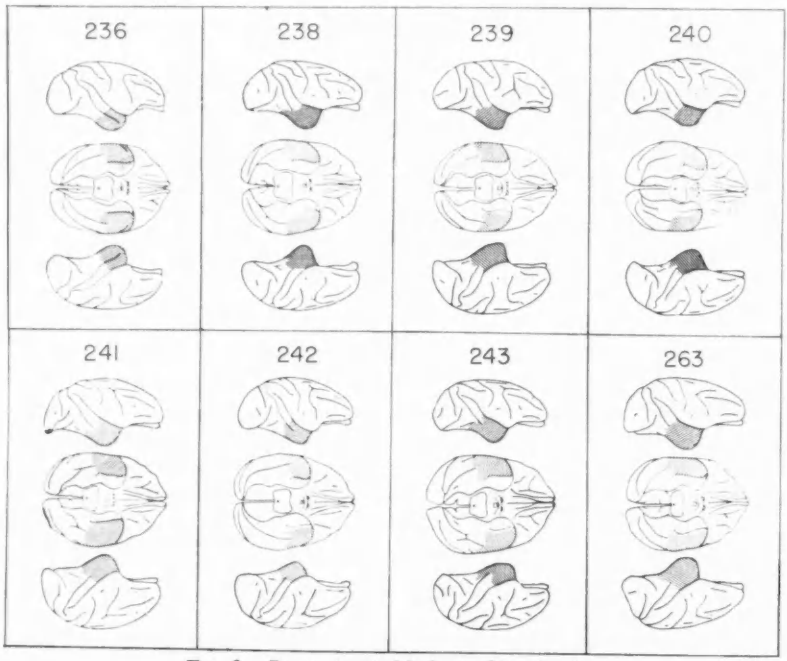

FIG. 3.—Reconstructed lesions of 8 animals.

Rostrally, the temporal polar cortex was completely removed. Laterally, the superior, middle and inferior temporal gyri were ablated up to a line perpendicular to a point half-way up the Sylvian fissure. This point is also defined by vertical projection of the end of the central sulcus upon the lateral fissure, and according to Woolsey and others, marks the rostral boundary of the auditory cortex. Thus, by observing this landmark, the auditory cortex in the superior temporal plane was spared. It is important to note that all grey matter forming the banks of the superior, middle and inferior temporal sulci was removed. On the other hand, sufficient white matter within the depths of the temporal lobe was spared to prevent (1) injury to the visual and auditory radiations in the wall of the ventricle, (2) perforation of the ventricular wall, and (3) damage to the surface of the hippocampus. The striatum and pallidum were both entirely free of damage. Insular cortex and claustrum[1] were also preserved.

As is well known, the rhinal fissure forms the boundary between neo- and palæocortex. The preservation of this boundary served as a criterion for the presence or absence of rhinencephalic damage. The histological studies indicated that injury to the medial bank of the rhinal fissure could entail damage to cortical, as well as subcortical, portions of the rhinencephalon. Three groups of animals were differentiated: (1) Those in which the rhinal fissure was entirely preserved, (2) those in which its lateral bank was destroyed, and (3) those in which both the medial and lateral banks had been removed. Involvement of palæocortex and possibly the claustrum or amygdala was present only in the

TABLE I.—PRIMARY DAMAGE TO TEMPORAL LOBE RHINENCEPHALIC STRUCTURES

Right Temporal Lobe	*236*	*237*	*238*	*239*	*240*	*241*	*242*	*243*	*263*
Prepyriform cortex	+	+	−	−	−	+	+	−	−
Entorhinal cortex	−	−	−	−	−	−	+	−	−
Insular cortex	−	−	−	−	−	−	−	−	−
Hippocampus	−	−	−	−	−	−	−	−	−
Claustrum	−	−	−	−	−	−	−	−	−
Lateral amygdaloid nucleus	+	−	−	−	−	−	−	−	−
Anterior amygdaloid area	−	−	−	−	−	−	−	−	−
Left Temporal Lobe									
Prepyriform cortex	+	−	+	−	−	+	−	−	−
Entorhinal cortex	+	−	−	−	−	−	−	−	−
Insular cortex	−	−	−	−	−	−	−	−	−
Hippocampus	−	−	−	−	−	−	−	−	−
Claustrum	−	−	+	−	−	+	−	−	−
Lateral amygdaloid nucleus	−	−	−	−	−	+	−	−	−
Anterior amygdaloid area	−	−	−	−	−	+	−	−	−

[1]Claustrum shows damage in the extreme ventrolateral portion in case 238 (unilateral) and 241 (unilateral).

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third group which consisted of 5 cases, in 3 of which the damage was unilateral. Damage to the palæocortex beyond the rhinal fissure never exceeded 2 mm. In view of the significance of these lesions, they will be described in detail.

Extent of Rhinencephalic Involvement (*Fig.* 4)

236: The right temporal lobe shows slight invasion of the prepyriform cortex between sections 180 and 250. In this area slight involvement of the lateral amygdaloid nucleus is also found; however, the encroachment is restricted to its most lateral edge.

On the left side, the dissection crosses the rhinal fissure damaging a small amount of the prepyriform and entorhinal cortex.

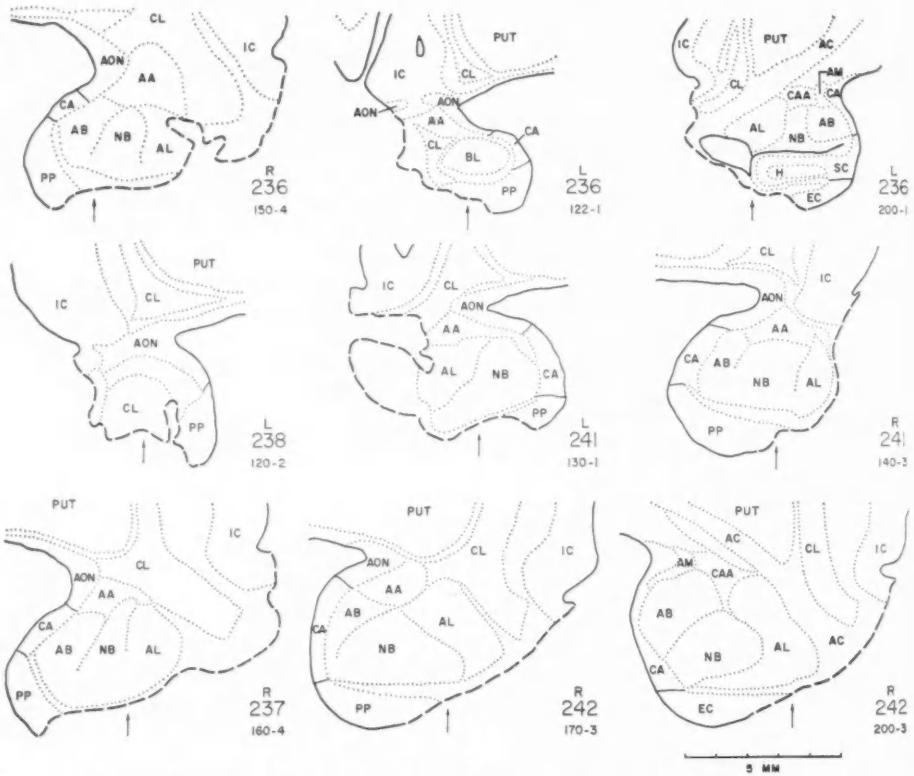

FIG. 4.—Reconstruction of rhinencephalic damage of *all* cases concerned. Dotted lines represent architectonic boundaries of grey matter and dashes represent surgical line of cleavage. The arrows mark approximate position of rhinal fissure.

238: On the left side rostrally, there is slight involvement in only a few sections of the prepyriform cortex and claustrum. Caudal to this area the rhinencephalon is intact.

241: On the right, the prepyriform cortex is invaded for a very short distance to about 1·5 mm. in depth between sections 100 and 130. Beyond this there is no damage to rhinencephalic structures.

On the left, the lesion follows approximately the same pattern except for a deeper invasion of the prepyriform cortex between sections 140 and 145. At this point there is slight encroachment upon the anterior amygdaloid area, ventrolateral tip of the claustrum, and the lateral amygdaloid nucleus.

242: On the right, the rostral superficial layers of the prepyriform and entorhinal cortex have minor lesions. Caudal to this the rhinencephalon is intact.

237: On the right, the prepyriform cortex is slightly invaded (about 2 mm. in depth) back to section 130. However, from this point on, the medial bank of the fissure is found intact, indicating complete sparing of the remaining entorhinal and prepyriform cortex.

In summary: Rhinencephalic involvement is extremely small. The hippocampus is not injured in any case. Damage to the amygdala is limited to the anterior amygdaloid area (unilateral in 1 case) and to the lateral amygdaloid nucleus (unilateral in 2 cases). Entorhinal cortex is injured slightly in 2 cases (both unilaterally). Somewhat more consistent damage is found in the prepyriform cortex. Of the 5 cases involved, 2 have bilateral and 3 have unilateral lesions. Again these lesions are indeed very small and involve the region beneath the temporal pole, where the transition between neo- and palæocortex is somewhat obscure.

In the 4 remaining monkeys there is no involvement of rhinencephalic structures. Their lesions fall within the boundaries outlined in fig. 3. Monkey 240 represents the greatest sparing of neocortex lateral to the rhinal fissure, with approximately 2 mm. of the neocortex remaining. The sum total of monkey 242's lesions represents the smallest cortical removal of the series. In contrast, monkey 263's lesions represent the greatest removal of the group.

III. Secondary Degeneration

A. *Retrograde degeneration of thalamic nuclei*

(1) *Pulvinar:* Degeneration was restricted to the posteromedial area (*see* fig. 5). This finding is consistent with earlier observations by Chow (1950), Simpson (1952) and Bucy and Klüver (1955). The corticopetal projection system of the pulvinar should not be confused with the corticofugal fibre tract described by Bucy and Klüver (1955), Whitlock and Nauta (1956) and others. Pulvinar and temporal neocortex are reciprocally

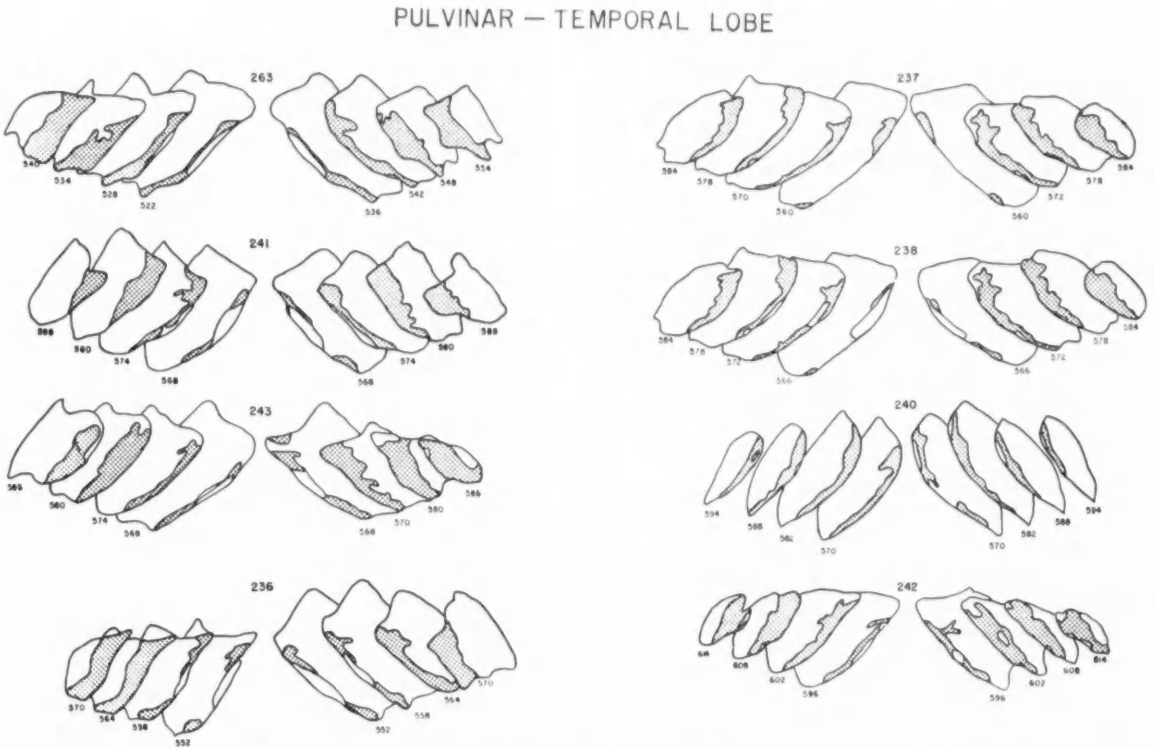

FIG. 5.—Serial cross sections of the pulvinar with cross hatching showing retrograde degeneration.

connected by these two tracts, which together form the classical "Bundle of Arnold."[1]

(2) *Medial geniculate body:* Degeneration was found in the caudal portion of the pars principalis. This again confirms observations made by Bucy and Klüver (1955). The problem arises as to the integrity of auditory cortex, and auditory radiations. Certainly, the auditory receiving area outlined with neurophysiological techniques by Woolsey and Walzl (*see* Woolsey and Fairman, 1946, fig. 6c) and by others was spared in all animals and there was no injury to its afferent radiations from the thalamus. The significance of the degeneration found in the posterior pole of the medial geniculate body will be discussed elsewhere (Akert, Woolsey, Diamond and Neff, 1961).

(3) *Lateral geniculate body:* No retrograde degeneration was found. This is in agreement with the absence of secondary degeneration throughout the visual radiation and supports the contention that the visual system was not encroached upon by the operative procedures.

B. *Degeneration of cortical and subcortical fibre connexions*

The detection of degenerative changes suffered noticeably from limitations of techniques. Only massive alterations, such as demyelinization and gliosis could be recognized in the Nissl and Weil stained sections. With degeneration time varying between 45 (case 237) and 230 days, it seemed impossible to differentiate between anterograde and retrograde direction. Nevertheless, several interesting facts were established. Since many of the connexions to be mentioned have been described and illustrated by either Bucy and Klüver (1955) or by Whitlock and Nauta (1956), it is unnecessary to give a detailed description and documentation of confirmatory data. However, the reader should be aware of the fact that the cortical ablations differed from those made by the two groups mentioned. The ablations of the former investigators were far more extensive and included rhinencephalon while the lesions of the latter were restricted to small neocortical areas of the temporal lobe.

(1) *Cortical connexions:* The anterior commissure, pars temporalis, was completely degenerated. This finding, together with the fact that no traces of degeneration were found in the body of the corpus callosum and in the tapetum, provides an excellent characterization of the extent of cortical ablations. Thus, one could state that "non-callosal temporal cortex" had been involved exclusively. Abundant fibre degeneration was

[1]Arnold, in 1838, illustrated this fibre tract as a component of the retrolenticular portion of the internal capsule and commented in his Atlas as follows: "fibrae coronae radiatae quae ad lobi inferioris apicem pertinent." It was Déjerine, who reinvestigated this important projection system in 1901 and credited its discovery to Arnold. It is not to be confused with Arnold's fronto-pontine bundle.

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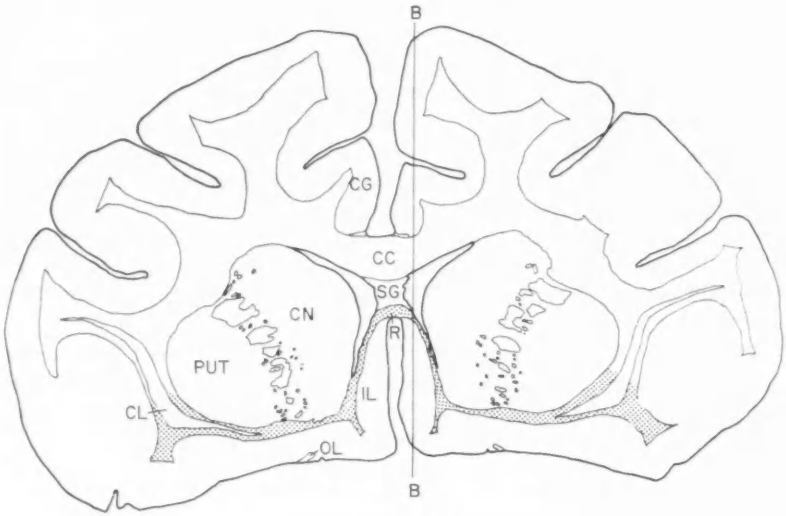

SECTION A

FIG. 6A.

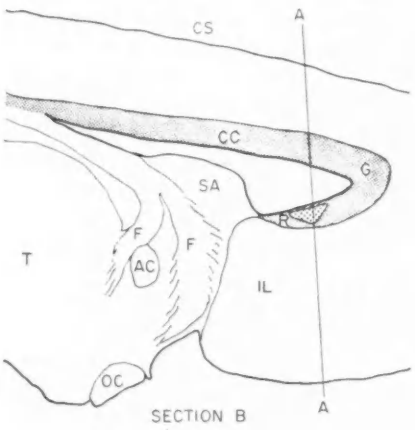

FIG. 6B.

FIG. 6.—Degeneration in uncinate system (*see also* figs. 8 and 9). A, Coronal section A showing degeneration in uncinate system and rostrum of corpus callosum (dotted area). Degeneration did not extend to the limits of white matter as drawn, instead thin bands of intact fibres were found surrounding it. Line B represents position of sagittal section B. B, Sagittal section B showing degenerated fibres within the rostrum of the corpus callosum (dotted area). Straight line (A) represents the position of coronal section B. A and B are not drawn at the same scale.

found in the white matter of adjacent parietal, posterior temporal and occipital lobes. A massive bundle of degenerated fibres could be traced to the posterior cingulate cortex (confirming Bucy and Klüver, 1955).

A most striking effect was the heavy degeneration of the uncinate system. It seems that the changes involved the same pathways described by Bucy and Klüver (1955). Thus, a major part of the uncinate fascicle—if not all—appears associated with neocortex rather than palæocortex of the temporal lobe. A clear-cut portion of this system instead of connecting with ipsilateral orbitofrontal cortex can be seen passing through the inferior part of the forceps minor and forms a portion of the rostrum of the corpus callosum (fig. 6). It then joins the uncinate system of the other side. Whether these fibres reach the homologous cortex of the contralateral temporal lobe or decussate to the orbitofrontal cortex could not be ascertained. The role of basal portions of the claustrum in the

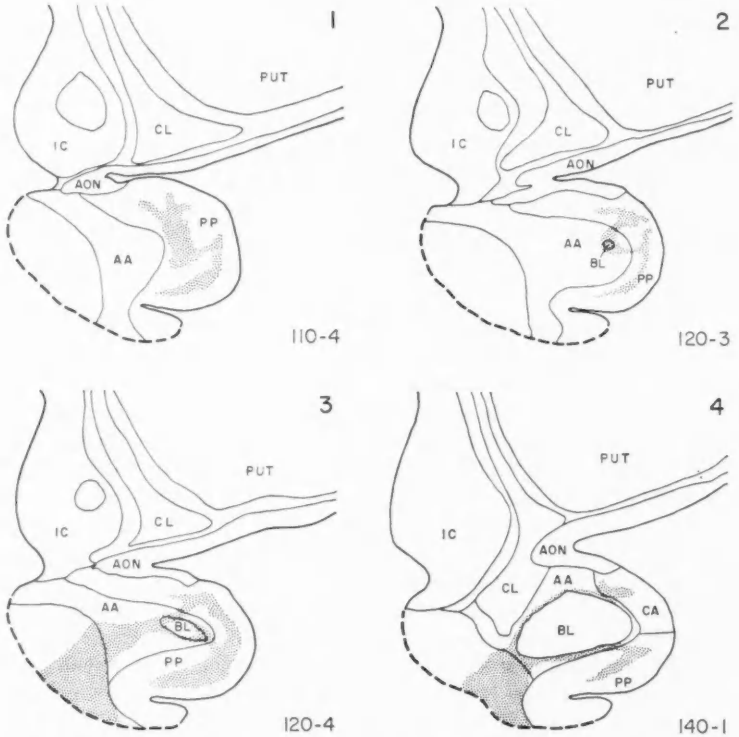

FIG. 7.—Fibre connexions of temporal pole and inferior temporal gyrus to amygdala and prepyriform cortex. Dotted area represents degenerated fibres.

uncinate system could not be clearly defined. Marked gliosis of this specific area could be due to the degeneration of fibres of passage. On the other hand, the presence of claustral synapses appears not unlikely in view of some degree of cell loss and chromatolytic cell changes that could be observed in the claustral areas adjacent to and intertwined with the uncinate fibre system.

Another important contingent of degenerated fibres was seen in the white matter of and entering the prepyriform cortex (fig. 7). Thus, a connexion between neotemporal cortex (presumably inferior temporal gyrus) and prepyriform cortex could be established. No traces of degeneration were found within the entorhinal cortex nor in the subjacent white matter.

(2) *Subcortical connexions:* The presence of degenerated tracts to pulvinar, medial geniculate body, superior colliculus and substantia nigra was confirmed. Of particular interest were degenerated fibres to the amygdala (fig. 7). These fibres pass within the white matter surrounding the amygdala dorsally and ventrally. As described above, some of these fibres enter prepyriform cortex, while the remaining portion is directed towards cortical amygdaloid areas.

The absence of degenerative changes may not be critical in view of the limited value of the techniques employed. Nevertheless, the lack of positive signs in fornix and stria terminalis seem to correlate with the absence of primary lesions in hippocampus and medial portions of amygdala.

Discussion

The experimental work concerned with "differential localization" of the Klüver-Bucy syndrome has met with many difficulties (Milner, 1954). A superficial review of the literature seems to lead to the conclusion that elements concerned with drives and emotions such as oral tendencies, loss of aggressiveness, and hypersexuality can be referred to the damage of the rostral half of the pyriform lobe (i.e. amygdala, prepyriform cortex and rostral portions of entorhinal area). On the other hand, the difficulties with visual learning and retention seem to be related to lateral and ventral cortex of the temporal lobe (*see* Table II). This correlation seems to be consistent with the traditional dichotomy of rhinencephalic and neocortical components and leads inevitably to the prediction that a group of animals with temporal lobe damage such as described in this study, should result in intellectual rather than emotional disturbances. However, this was not true. While symptoms of psychic blindness (described and discussed in detail in a separate publication by Meyer, 1958) were present, the animals also unmistakably showed signs of

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TABLE II.—LOCALIZATION OF FOUR SYMPTOMS IN THE KLÜVER-BUCY SYNDROME WITH HISTOLOGICAL VERIFICATION

Symptom	*Localization*	*Animal*	*Author*
I. Increase in oral tendencies (hypermetamorphosis)	Pyriform lobe* and hippocampal tip	Cat	Schreiner and Kling (1953)
	Entorhinal area (with encroachment of amygdala, hippocampus and prepyriform area)	Phalanger	Adey, Merrillees and Sunderland (1956)
II. Hypersexuality	Pyriform lobe* and hippocampal tip	Cat	Schreiner and Kling (1953)
	Pyriform lobe*	Agouti, Lynx	Schreiner and Kling (1956)
	Rostral half of pyriform cortex sparing amygdala	Cat	Green, Clemente and de Groot (1957)
III. Tameness	Entorhinal area with encroachment of amygdala, hippocampus and prepyriform area	Phalanger	Adey, Merrillees, and Sunderland (1956)
	Anterior pyriform lobe and adjacent neocortex	Monkey	Walker, Thomson and McQueen (1953)
IV. "Psychic Blindness" Loss of retention in visual discrimination but no deficits in relearning a visual problem	Lateral temporal neocortex	Monkey	Chow (1952)
Severe deficits in retention and relearning of visual discrimination problem	Ventral temporal neocortex	Monkey	Mishkin (1954)

*The term "pyriform lobe" as used in this paper includes the superficial (prepyriform and entorhinal cortex) as well as the deep grey matter (amygdala).

"hypermetamorphosis" and lack of fear.[1] The explanation of this apparent discrepancy becomes of interest.

First of all, did the lesions spare the rhinencephalon? The hippocampus was totally intact in all animals and encroachment upon prepyriform and entorhinal cortex together with laterobasal amygdala was extremely small. Rhinencephalic involvement of such minimal degree seems to have no detectable effect on behaviour, since the partial Klüver-Bucy syndrome was present to the same degree in all 9 animals, of which 4 (236, 237, 241, 263) had no rhinencephalic involvement at all, and 3 (237, 238, 242) had very slight damage to rhinencephalic components on one side only. The conclusion seems justified that encroachment on rhinencephalic structures in the present series of animals was functionally insignificant.

The next problem is concerned with the regions of the neotemporal cortex crucial to the release of oral behaviour and the production of the taming effect. No definitive answer can be given as yet; however, suggestions can be made from the study of fibre connexions. Of particular interest are the relationships with rhinencephalic structures, known

TABLE III.—CONNEXIONS BETWEEN NEOCORTICAL AND RHINENCEPHALIC PORTIONS OF THE TEMPORAL LOBE

Neocortex	*Rhinencephalic*	*Animal*	*Author*	*Method*
Superior temporal gyrus Middle temporal gyrus	Lateral amygdala, hippocampal gyrus, and hippocampus	Monkey	Segundo, Naquet, and Arana (1955)	E
Inferior temporal gyrus	Basal lateral amygdala, periamygdaloid cortex and hippocampal gyrus	Monkey	Whitlock and Nauta (1956)	A
	Prepyriform cortex	Monkey	Petr, Holden and Jirout (1949)	E
Temporal pole	Amygdala and hippocampus	Monkey	Pribram, Lennox and Dunsmore (1950)	E
	Amygdala	Cat	Gloor (1955)	E
	Amygdala, hippocampus and hippocampal gyrus	Monkey	Segundo, Naquet and Arana (1955)	E
	Amygdala	Man	Ludwig and Klingler (1956)	A
	Prepyriform Cortex	Monkey	Petr, Holden and Jirout (1949)	

E refers to electrical stimulation methods including strychnine neuronography.
A designates anatomical studies.

[1]The absence of hypersexual behaviour in our animals may suggest that this phenomenon cannot be produced by neotemporal lesions. On the other hand, we would like to point out that the monkeys were not sexually mature and that no special efforts were made to study sexual behaviour.

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to control oral and defensive behaviour. As shown in Table III the temporal polar region (designated TG by Bonin and Bailey, 1947) maintains intensive connexions with amygdala, prepyriform cortex and entorhinal area. This region was consistently, but not exclusively, damaged in all experimental animals. Pribram and Bagshaw (1953) seem to be the only investigators who attempted the crucial ablation; however, they inadvertently damaged the amygdala in addition to the cortex of the polar region.

Another neotemporal area with rhinencephalic connexions is the inferior temporal gyrus. As shown in our own material, this area has pathways to amygdala and prepyriform cortex and according to some authors, it is also related to entorhinal area (Table III). Again, direct evidence, showing that ablations of the rostral part of the inferior temporal gyrus may induce tameness and hyperorality, is not available.

One can only guess that neotemporal areas, on the basis of the above-mentioned fibre connexions, exert a significant influence on the excitability of rhinencephalic structures, and if so, their desctruction may entail behavioural changes not unlike those seen when rhinencephalic areas are themselves removed.

Schneider and Crosby (1954) have shown by means of electrical stimulation that the lateral aspects of the temporal lobe in the monkey may contain a motor representation of facial and masticatory musculature similar to the one demonstrated in the amygdala by MacLean and Delgado (1953) and several subsequent investigators. Also, Magnus, Penfield and Jasper (1952) were able to elicit masticatory fits by electrical stimulation of the temporal polar region in patients. Finally, by evoking memories with emotional contents from the lateral aspects of the temporal lobe in epileptics, Penfield (1958) has given further indication that the neocortical and rhinencephalic portions of the temporal lobes are closely interrelated.

This explanation of our own results, based on intratemporal association systems, is not unexpected. Actually, it seems to work both ways, since rhinencephalic damage has been shown to cause or increase visual discrimination difficulties. Perhaps one might expect a difference in degree between the rhinencephalic and neotemporal types of Klüver-Bucy syndrome. Such a difference exists indeed. In the classical studies of Klüver and Bucy the hyperorality, tameness and hypersexuality were permanent (Klüver, 1952), whereas our animals showed signs of gradual return to normality. Only the "psychic blindness" (even though not observed over a long enough period of time) seems to be enduring. The nature of this difference is not clear.

SUMMARY

(1) Bilateral ablations of neotemporal cortex in 9 monkeys (*Macaca*

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mulatta) produced a Klüver-Bucy syndrome, consisting of deficiencies in visual discrimination learning and retention, increase of oral tendencies, and tameness. These symptoms developed sharply after the operation and diminished noticeably after approximately three months.

(2) The lesions were remarkably uniform throughout the group. Visual radiations and auditory receiving areas, except for the rostral borders, remained intact. Rhinencephalic involvement was absent in 4 animals. In 5 there was minimal damage to the lateral amygdaloid nucleus, anterior amygdaloid area and prepyriform cortex near the temporal pole. The ablations consistently included the area TG, that is, neocortex of the temporal pole.

(3) Secondary degeneration was absent in fornix and stria terminalis. Complete degeneration of the temporal portion of the anterior commissure and absence of degeneration in the body and forceps major of the corpus callosum further characterize the extent of neotemporal damage. Particular significance was attributed to the degeneration of fibres to the amygdala and prepyriform cortex, to the posterior cingulate gyrus and to the uncinate system, since these structures are known to play a significant role in the control of oral and defensive behaviour.

(4) The significance of this study seems to lie in the further demonstration of close functional and anatomical relationship between rostral "association cortex" of the temporal lobe and the rhinencephalon.

The authors wish to acknowledge the valuable assistance of Miss Helen Brandemuehl in the preparation of the histological material, and the help of Dr. G. M. French in the reconstruction of cortical lesions during the initial stages of this work.

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LEGENDS TO PLATES

PLATE L

FIGS. 8 and 9.—Photomicrograph of Weil stain showing demyelinization in rostrum of corpus callosum and forceps minor compared with normal section at approximately the same level (*see also* fig. 6).

PLATE LI

FIGS. 10 and 11.—Neocortical ablation at midlevel of amygdala compared with normal section at approximately the same level below.

PLATE LII

FIGS. 12 and 13.—Neocortical ablation at level of hippocampus (rostral pole) compared with normal section at approximately the same level below.

TABLE OF ABBREVIATIONS

A	Amygdaloid nuclear complex	F	Fornix
AA	Anterior amygdaloid area	G	Genu of corpus callosum
AB	Accessory basal amygdaloid nucleus	H	Hippocampus
		IC	Insular cortex
AC	Anterior commissure	IL	Infralimbic cortex
AL	Lateral amygdaloid nucleus	NB	Basal amygdaloid nucleus
AM	Medial amygdaloid nucleus	OC	Optic chiasm
AON	Anterior olfactory nucleus	OL	Olfactory tract
BL	Basal lateral nuclear complex (amygdala)	PP	Prepyriform cortex
		PUT	Putamen
CA	Cortical amygdaloid nucleus	R	Rostrum of corpus callosum
CC	Corpus callosum	RF	Rhinal fissure
CG	Cingulate gyrus	SA	Septal area
CN	Caudate nucleus	SC	Subicular cortex
CS	Cingulate sulcus	SG	Subcallosal gyrus
CAA	Central amygdaloid area	SF	Sylvian fissure
EC	Entorhinal cortex	T	Thalamus

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PLATE L

FIG. 8.

FIG. 9.

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PLATE LI

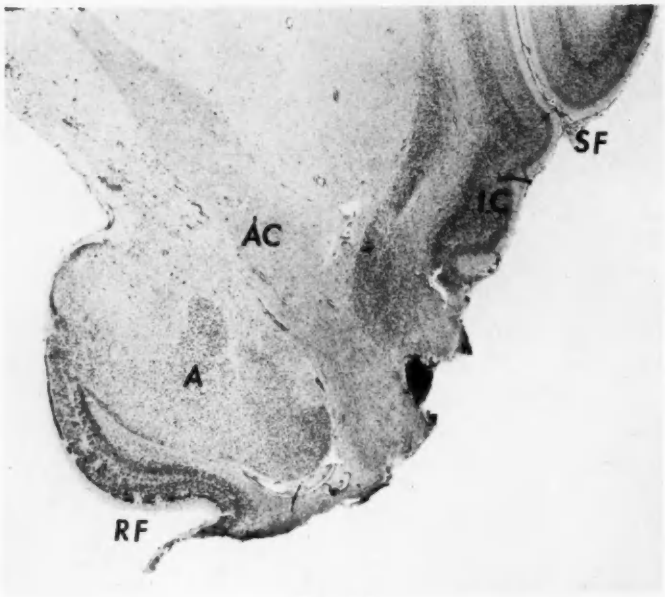

FIG. 10.

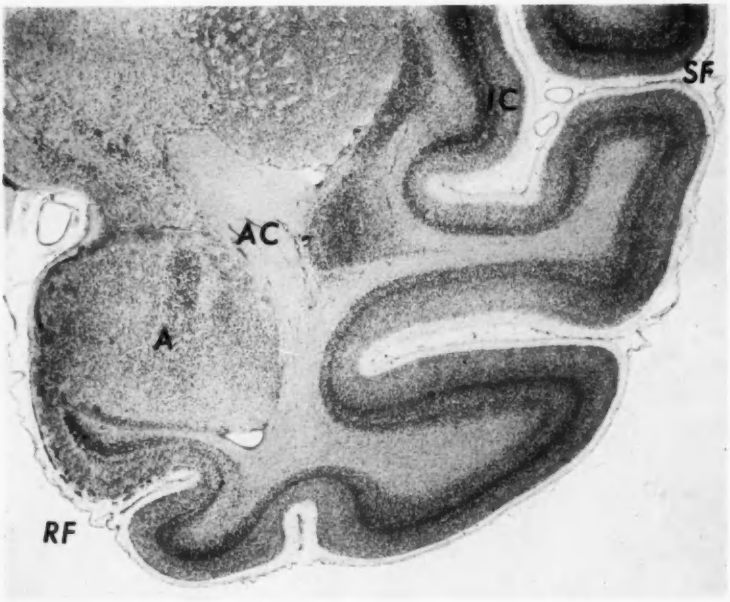

FIG. 11.

To illustrate article by K. Akert, R. A. Gruesen, C. N. Woolsey and D. R. Meyer.

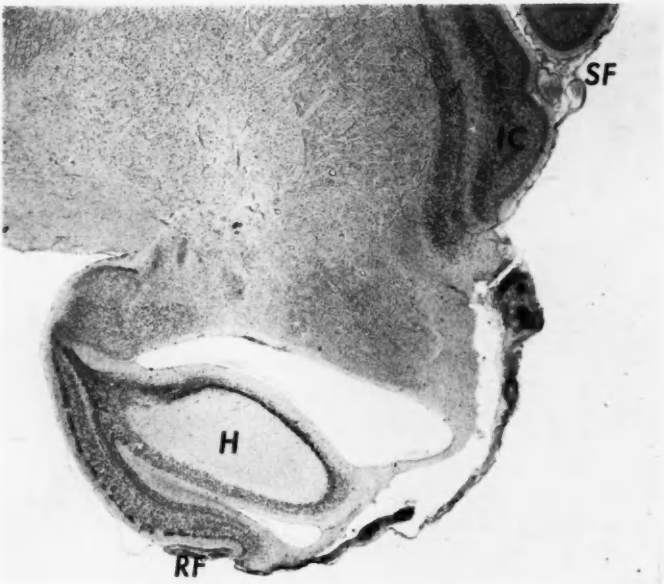

FIG. 12.

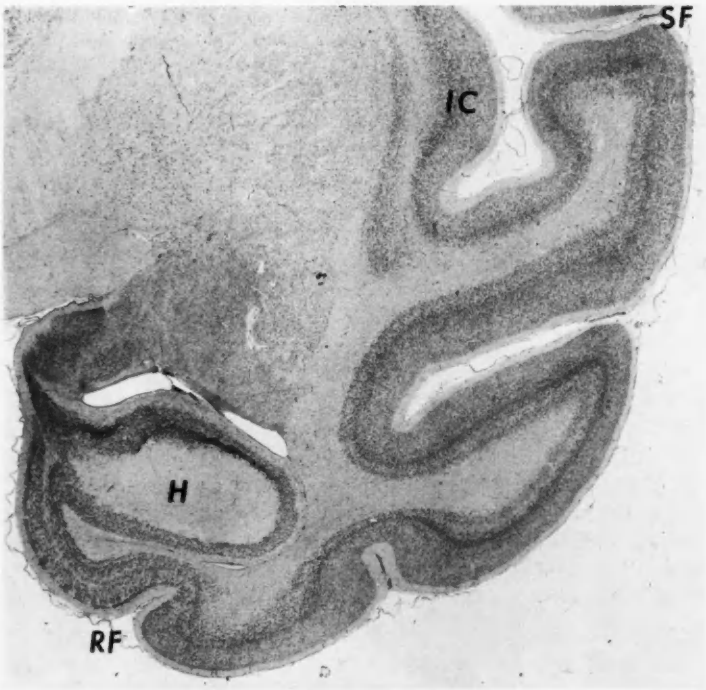

FIG. 13.

To illustrate article by K. Akert, R. A. Gruesen, C. N. Woolsey and D. R. Meyer.

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THE RELATIONSHIP BETWEEN TERMINAL LINGUAL INNERVATION AND GUSTATION

A Clinical and Histological Study

BY

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The primary objective of this investigation was to undertake a reappraisal of the role of terminal nerve fibres in relation to the distribution and specificity of the four main types of taste transduced by the human tongue.

Such a reappraisal appeared called for from a survey of the facts available on the subject. Firstly, textbooks on histology appeared to be engrossed with the taste bud, which was often referred to as "the organ of taste," and was considered to be the sole peripheral receptor for the sense of taste (Maximow and Bloom, 1952). Only the nerve filaments ending within the taste buds ("intragemmal") were stressed. Commencing with the earliest observations of Loven and Schwalbe in 1867, a large number of distinguished histologists (e.g. Retzius, 1892; von Lenhossek, 1893; Ebner, 1899) had studied the terminal ramifications of the ninth cranial nerve in the lingual mucosa with silver impregnation techniques. Ehrlich (1886) and Cajal (1899) had also done the same employing vital staining with methylene-blue. Most of these observations were on the nerves of the foliate papilla of the rabbit tongue. While all these workers had described intragemmal as well as peri- and inter-gemmal freely ending nerve filaments as the terminal ramifications of the glossopharyngeal nerve, the taste-bud or, more specifically, the gustatory cell still appeared to hold sway as the only peripheral mechanism subserving gustation. Until recently, the significance of intergemmal nerve fibres, of lingual papillæ without taste buds, and of the gustatory innervation of the lingual mucosa in general, did not appear to have been appreciated. Striking observations such as those of Pfaffmann and Bare (1948) that rats continue to distinguish between sodium chloride solutions and water, and do not exhibit complete ageusia to quinine (Patton, 1950) even after section of the gustatory nerves with

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consequent complete degeneration of the lingual taste buds, had remained unexplained.

Secondly, coming to clinical observations, since the end of the last century the concept of four primary tastes seems to have developed, out of the earlier notions of nearly a dozen basic tastes (Geldard, 1953). The other current idea about gustation in man, prevalent since the work of Hänig (1901) and others, concerns the localization of specific taste qualities over different regions of the tongue, such as bitter at the back, sweet at the tip and sour at the sides. Somewhat at variance with this alleged localizing phenomenon are the old but carefully performed clinical tests of Oehrwall (1891) and of Kiesow (1898) on individual fungiform papillæ. Some papillæ were not responsive at all, the majority were sensitive to more than one type of taste, while a few appeared specialized. Since there is no histological difference in the taste buds or their pattern of innervation, within one papilla or among different types of papillæ, the presence of various submodalities of taste remains unaccountable from a consideration of the histology of the gustatory receptor. This lack of histo-clinical correlation appears to have disconcerted students of gustation who have been conditioned, by nineteenth century morphologically oriented thinking, to equate a specific modality or quality of sensation to one specific type of peripheral receiving or analysing mechanism or "end-organ."

One of the motivating factors behind this present attempt at reappraisal of gustation was our previous experience in another related field, viz. cutaneous sensation (Dastur, 1955). An extensive study of human skin with normal and impaired sensibility had revealed the essential histological identity of nerve fibre terminals subserving all the so-called modalities of cutaneous sensation. Whether arising out of the perifollicular nerve basket and ending on the hair sheath, or emerging from the interfollicular nerve nets and terminating in the dermis, the final neural arborizations were invariably "free nerve endings." Organized encapsulated neural end-organs were never encountered in any part of the hairy skin of man. Similar observations have also been reported by the Oxford School of Anatomy (Sinclair *et al.*, 1952, and Weddell *et al.*, 1955). In the light of these studies we expected nothing but an essential simplicity and identity of terminal nerve fibre pattern among the various papillæ and on the different regions of the tongue, irrespective of the quality of taste most readily evoked from a region. It remained, however, to varify this by a composite clinico-histological study. Finally, it was also intended to check in the field of gustation our earlier observation on cutaneous sensation that maximal sensory acuity resided in areas of maximal nerve fibre density.

With these objectives in view it was planned to carry out the investigation in two parts: (1) A clinical mapping of different areas of the tongue, for each of the four primary tastes, attempting a quantitation of the response evoked by the gustatory stimuli in all the subjects tested. (2) A histologi-

cal study of the mucous membrane of different parts of tongues obtained at autopsy, especially with a view to comparing the pattern and density of terminal nerve fibres in different papillæ and regions.

Material and Methods

All the normal volunteers selected for participation in the clinical aspects of the present study were graduate students and research workers of the laboratories of the Indian Cancer Research Centre and the Tata Memorial Hospital. They ranged in age from 21 to 42 years. 62 of a total of 65 subjects tested were included in the final evaluation (Table I). For each subject, only one, or at the most two, qualities of taste were tested on any one day. The solutions to be tasted were first tried out on a

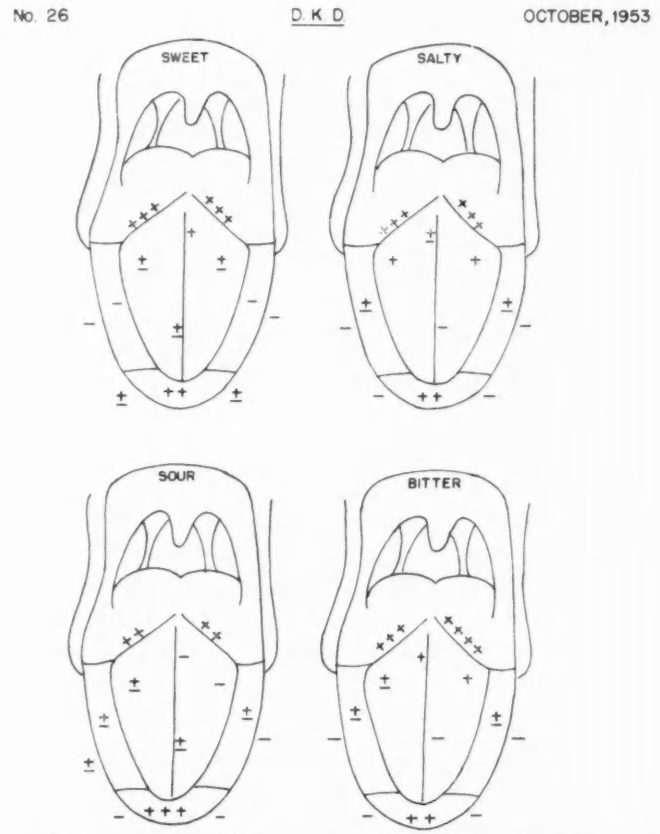

Diagram 1 : Four outlines of the tongue and fauces indicating the "quantitative" response of one of the subjects to the four test solutions on different parts of the tongue. (The signs *outside* the tongue, indicating the response at different spots on the floor of the mouth, are not considered in the text.)

few subjects, and the concentrations employed were such as to make the solutions fairly strongly sapid in amounts of a drop or two. The final test solutions were 0·5 per cent quinine, 2 per cent acetic acid, 5 per cent sodium chloride and 10 per cent sucrose.

For the clinical test a chart with 4 outline-drawings of the tongue, fauces and soft palate (Drawing) was used in each case. As seen therein, the surface of the tongue was demarcated into different zones, such as the tip, sides, dorsum of anterior two-thirds, the circumvallate papillary area, and posterior one-third. Response of the subject to each of the four gustatory stimuli was recorded on one of the four drawings. He or she was advised to keep the tongue extruded: wherever possible, the area to be tested was wiped dry by the examiner. A small drop of the test solution was then deposited on it and the subject decided on the degree of response, according to previous instruction, *before* withdrawing the tongue in the mouth and spitting or swallowing, as the case might be. As far as was feasible, he was advised to spit rather than swallow the test drop, and he was allowed to gargle his mouth with water before another drop of the same test solution was deposited on another area of the tongue or mouth.

The subject was previously instructed to respond to the strength of the gustatory stimulus felt by him, in a semi-quantitative manner along a scale of zero to four. Thus the maximal response evoked by any stimulus at any spot was to be designated 4 plus (++++). A negative (− or 0) response indicated failure to appreciate any taste at all from that region, even though the subject was previously informed of the taste being tested. Plus 1 (+) to plus 3 (+++) responses were intermediate grades between the above two extremes.

The bulk of the material for the histological examination came from cadavers. Entire tongues, including—in many cases—faucial pillars and the epiglottis were removed at autopsy and fixed in formalin. Of the 26 tongues so obtained, in 11 the number of different types of lingual papillæ at different areas were counted with the aid of a magnifying glass.

In most cases, tissue for sectioning was given from the tip, one side (including edge and part of dorsum of anterior two-thirds), the area of circumvallate papillæ, the posterior one-third of the tongue and occasionally, the free margin of the epiglottis. The paraffin sections were stained in all cases with modified Masson's Trichrome and with Mallory's aniline blue, since both these stains bring out adequately the distinction between nerve fibre elements and other types of connective tissue. The plane of the sections was invariably at right angles to the mucous membrane, so as to bring out clearly the structure of the papilla and of the taste buds.

In 14 of the tongues, nerve fibres were further studied by Holmes's silver staining for 15 to 25 μ thick paraffin sections, and in one instance, Gros-Bielschowsky's silver technique was employed for frozen sections of different areas sectioned in various planes.

It was also possible to stain *in vivo* with methylene-blue the tongues of 5 rats and 3 rabbits, while the animals were under anæsthesia prior to being killed. The method followed was the one employed previously for skin and for muscle (Dastur, 1955 and 1956). Both the lingual mucosa and the subjacent muscle were injected uniformly with 0·025 per cent methylene-blue. After twenty-five to thirty minutes, portions of the mucosa with the immediately subjacent muscle fibres were sliced off the tongue using a safety-razor blade. These portions were then fixed, dehydrated, cleared, mounted and studied as "whole mounts," no further sectioning being done (method identical to that described previously).

Observations

A. *Clinical observations.*—These are summarized in Table I. The figure in each case gives the "total score" for a particular taste for a given

area, for the group of subjects as a whole (62). Since the individual responses to the various gustatory stimuli are necessarily subjective, a formal statistical evaluation could not be applied to the scores. However, the statistician advised that a completely random division of the subject population should be undertaken (by the toss of a coin) and the total score of the whole group should be compared to the total scores of the two sub-groups so obtained. The latter would indicate the "scatter" of "values" and provide a check on the former. Two such random sampling procedures were carried out, and the difference between the total values of the two sub-groups of the whole group (for a given taste at a particular site) was found to range from 2 per cent to about 25 per cent. The average difference was of the order of about 10 per cent. Thus, for example, for the sweet taste at the circumvallate zone, the total scores for two random sub-groups were 118 and 131, respectively, the total score for the whole group being 124·5. The limits of variability being roughly defined in this fashion it was felt that the individual values for the whole group (as given in Table I) were adequately representative of the gustatory acuity of the parts of the tongue stimulated by the sapid solution in question.

TABLE I.—"QUANTITATIVE" EVALUATION OF GUSTATION IN MAN

		Score in different areas and for the whole tongue (62 subjects)				
Taste	*Sapid solution*	*Dorsum of tip*	*Sides*	*Centre of anterior 2/3*	*Circum-vallate zone*	*"Whole tongue"*
Sweet	10% sucrose	104·5 (+28)* 132·5	48·5 (+14)* 62·5	40·5 (+12)* 52·5	124·5 (+38)* 162·5	79·5 (+23)* 102·5
Salty	5% NaCl	121·5	62·5	59·0	179·5	105·6
Sour	2% acetic acid	151·0 132·5	69·0 62·2	46·0 52·2	127·5 162·8	98·9 102·6
Bitter	0·5% quinine	125·0	55·0	51·5	181·5	103·2
All tastes		132·5	62·3	52·3	162·7	102·6
Rating		II	III	IV	I	

*Correction factors

The data for the "Whole Tongue" (last column of Table I) may be considered first. The scores for salty, sour and bitter tastes are very close to one another, around a hundred, but the score for the sweet taste falls apart being about 20 per cent less than that for the others. So it becomes apparent that 5 per cent sodium chloride, 2 per cent acetic acid and 0·5 per cent quinine solutions are comparable in terms of the quantitative gustatory response which they evoke in normal young subjects, but that 10 per cent sucrose is not adequate in concentration to evoke an equivalent

response. If the strength of the sugar solution had been a little more than 10 per cent, it would probably have become comparable to the other three. To make the figures for the four tastes comparable, the addition of (+23) to the score for sweet for the Whole Tongue and of corresponding amounts to the scores for the four main regions, is required as a sort of "correction factor" (first line of Table I).

Secondly, the rating of the four different regions of the tongue for their overall gustatory acuity might be examined (last two rows of the table). The zone of circumvallate papillæ (score of 163) appears over 50 per cent more sensitive or more appreciative of taste in general than the tongue taken as a whole (score of 103). Similarly, the tip of the tongue would appear to be about 25 per cent more sensitive with a score of 133. On the contrary, the sides of the tongue (score of 62) and the centre of the anterior two-thirds (score of 52) seem to transduce gustatory stimuli only about half as well as the tongue as a whole, and three times as poorly as the circumvallate zone. The significance of these observations will be considered later, while describing the histological findings.

Coming now to individual tastes at specific areas (and considering the corrected scores for sweet), it is seen that at the tip the order of decreasing appreciation is Sour (151)> Sweet (132)> Bitter (125)> Salty (121). For the sides and edges of the tongue, the order is Sour (69)> Sweet and Salty (62 each)> Bitter (55). For the centre of the anterior two-thirds of the tongue, the order is Salty (59)> Sweet and Bitter (about 52 each)> Sour (46). At the circumvallate zone the order is Bitter and Salty (about 180 each)>Sweet (162)>Sour (127).

The most prominent feature of these observations is that the circumvallate zone and the tip gave far higher scores for the four gustatory qualities than any other area of lingual mucosa. Rigid specificities between site and taste were not encountered. Thus, at the back (the circumvallate zone), both bitter and salty tastes evoked the same degree of response, and even sweetness appeared better appreciated here than anywhere else, when gustatorily comparable strengths of the testing solution were used. Further, it was sourness rather than sweetness that was best mediated from the tip of the tongue which has customarily been reserved for the sweet taste. On the contrary the tip transduced even the quality of bitterness quite well, with a sensitivity about 25 per cent more than that for the tongue as a whole. Yet another clinical feature of the present set of data which is at variance with the usually accepted ideas concerns gustatory acuity of the side and edge of the tongue. The response to each of the four tastes from this site was quite poor; in fact, only a little better than that evoked from the mucosa of the centre of the anterior two-thirds which has proved itself to be relatively the most irresponsive part of the lingual surface.

B. *Morphological observations.*—These consist of a rough counting of the

three or four main varieties of lingual papillæ on different parts of the tongue, and are summarized in Table II. There are only two points to be noted. Firstly, that the circumvallate zone includes both vallate and circumvallate papillæ, the latter preponderating, and that this area is almost devoid of any other type of papilla. Secondly, the tip of the tongue bears four to six times as many papillæ as the centre or the sides of the tongue, in relation both to the total number of papillæ in general and to the number of fungiform papillæ in particular.

TABLE II.—AVERAGE COUNTS OF LINGUAL PAPILLÆ ON DIFFERENT REGIONS OF 12 TONGUES

Papillæ	*Tip*	*Sides*	*Centre Ant. 2/3*	*Circum-vallate*	*Posterior third*
Filiform	7	4	10	—	Unclear
Fungiform	84	13	16	—	
Circumvallate +vallate	0	0	0	15	

Even these cursory observations on papillary counts indicate that the areas of maximal gustatory acuity—the circumvallate zone and the tip of the tongue—are characterized by relatively dense accumulations of circumvallate and of fungiform papillæ, respectively. The next logical step was to see if the gustatory sensibility could be correlated to (i) the density of innervation of these papillæ, or (ii) their taste-bud population, or (iii) a combination of these two, or (iv) some other histological characteristic of the papillæ or the lingual mucosa of these two areas.

C. *Histological observations: on the human tongue.*—In sections stained with Masson's trichrome or Mallory's aniline blue, the most relevant histological feature was the presence of prominent neural elements in the submucosa of the circumvallate papillæ and of the fungiform papillæ at the tip. The entire core of the circumvallate papilla appeared filled by a tuft of endoneurial and perineurial fibres, with their characteristic wavy contours and slender fusiform nuclei (fig. 1, Plate LIII). These tufts reached up to the epithelium in the centre of the papilla, but were not conspicuous at the sides where, generally, the taste buds abounded. Occasionally, medium-sized neurons were encountered in these tufts. An essentially similar, though less striking, picture was noticed in relation to the nerve tufts in the centre of the fungiform papillæ on the dorsum of the tip of the tongue. Over the lingual mid-dorsum and in other areas devoid of papillæ nerve fibre elements were very scarce, the submucosa here being filled up with clumps and bundles of collagen.

The nerve fibres themselves were clearly visualized by silver impregnation techniques. 30 μ thick Gros-Bielschowsky preparations revealed either small coils and twigs of nerves going up into the papilla, or more complex tufts and clusters formed of a larger number of nerve fibres, also tending to

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reach up to the epithelium (fig. 2). These features were very well seen in fungiform papillæ on the tip and in circumvallate papillæ, transverse sections through which revealed a maze of fibres throughout the core (fig. 3). In either view, axon filaments terminating freely in the deeper layers of the epithelium or in the subepithelium were witnessed (figs 2–3). Organized or encapsulated neural "end-organs" were not observed. The appearance of the papillary innervation was very similar to that pictured in the beautiful drawing (fig. 186) by Cajal (1899) of the "submucous plexus" and terminal neural arborization in the papillæ on the anterior part of the cat's tongue. In general, the subpapillary nerve twigs consisted predominantly of thick fibres with only a few thin fibres (fig. 4), while the intrapapillary nerve fibres were, for the greater part, thinner. It was surmised that the latter were ramifications of the thicker fibres, and this was proved when a thick stem fibre was seen to arborize terminally into several delicate axon filaments (fig. 4). The picture was comparable to the appearance of branching Stem axons observed in the skin (e.g. fig. 4 of Dastur, 1955).

15–20 μ thick paraffin sections impregnated by Holmes's method also brought out adequately the same features of papillary innervation. While almost every papilla on the dorsum of the tip was richly innervated, the innervation of the small epithelial protrusions on the undersurface of the tip was scanty and inconstant. However, when nerve fibres were encountered in these regions, their appearance, course and termination were comparable to those in the fungiform papillæ (fig. 5), the ending also being in relation to the epithelial cells.

Sections through the posterior surface of the tongue were also characterized by a paucity of nerve fibres, as compared to the dorsum of the tip and the circumvallate zone. Within the large vallate papillæ as also in the subjacent submucous tissue (often containing mucus glands or lymphoid follicles), only small scattered nerve twigs were encountered.

As regards the presence of taste buds, only the circumvallate papillæ revealed them with any consistency. Even the dorsum of the tip of the tongue with its high degree of gustatory acuity failed to reveal taste buds in the fungiform papillæ, except on rare occasions. Although serial sections were not made through a single papilla on any part of the tongue, representative parts of *several* adjacent papillæ were examined in each block of tissue through the variously stained sections. Sections through the vallate papillæ on the posterior third of the tongue also did not show any taste buds. Thus, even granting the possibility of some taste buds occasionally going undetected with the histological methods adopted, it appeared that for the human tongue as a whole, taste buds constituted a prominent and fairly constant feature of the circumvallate papilla only.

D. *Relationship between structure and function.*—In order to answer the important problem of the correlation of gustatory sensibility and its

acuity to one or more histological characteristics of the lingual surface, it was considered essential to make a *rough* quantitative assessment of the density of submucosal and papillary innervation and of the taste buds on different parts of the tongue, and to compare this with the rough quantitation previously carried out for the clinical sense of taste (Table I). The histological grading was as follows: (++) or 2 if there were many nerve fibres or large nerve tufts or many taste buds throughout the structure or section examined; (+) or 1 if there were prominent nerves only in some parts of a section or in some papillæ only, or only a few taste buds; (±) or $\frac{1}{2}$ if there were only an occasional nerve fibre or taste bud in the part in question; and (−) or 0 if there were not a single nerve fibre or taste bud in the section. The average "values" and the histoclinical correlation are summarized in Table III.

TABLE III.—APPROXIMATE VALUES FOR DENSITY OF NERVE FIBRES IN DIFFERENT PARTS OF 26 TONGUES—AND A HISTOCLINICAL CORRELATION

	Dorsum of tip	*Centre and sides. Ant. 2/3*	*Circumvallate zone*	*Posterior third*
Nerves in papillæ	34·5	9·5	32·5	9·0
Nerves in submucosa	27·0	8·5	28·0	13·0
Gustatory acuity	132·5	57·3	162·7	—

From this it is at once apparent that the circumvallate zone and the dorsum of the tip are comparable to one another in their overall nerve fibre density, and also in their gustatory acuity for sapid solutions in general. However, these two regions differ markedly in respect of their taste bud density. In fact, even in the circumvallate zone, the density of innervation was much more impressive than that of taste buds, for the group as a whole: only 14 of the 26 tongues examined revealed taste buds in this zone, in several random sections. Over the centre and sides of the anterior two-thirds, as also over the posterior third of the tongue, the epithelial surface was more smooth than papillary, and the density of innervation was roughly three to four times less here than in the other two zones mentioned above. Once again, there was a fair histoclinical correlation, the gustatory sensibility for the centre and sides being about three times less than the acuity for taste over the circumvallate zone (Table III). The tentative conclusion that seems inescapable is that the most constant and reliable histological substrate for transducing the sense of taste from the human tongue is the nerve fibre population of its papillæ and its submucosa.

E. *Neurohistology of lingual mucosa in animals.*—This was confined to a few rats and rabbits, and the only technique employed was intravital staining with methylene-blue, since the objective was merely to confirm the nature of the terminal ramifications of nerve fibres in the lingual mucosa of mammals.

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Fig. 6 shows a nerve net in a "whole mount" of mucous membrane over the anterior third of the rat's tongue. Some of the superficial fibres of the lingual muscles almost invariably remain attached to greater parts of the mucosa when it is pared off the rest of the tongue. A small but clear motor end-plate is seen on one such striated muscle fibre in the lower part of this figure. In the right upper quadrant, branches of the main nerve trunk are seen deploying out with at least one axon filament ending freely. In other parts of the rat tongue the innervation was less profuse, but the mode of ending of the nerve fibre was always the same. Whether this was in the mucous membrane or in the submucosa could not be ascertained from whole mounts.

Similar preparations of mucous membrane of the rabbit tongue reveal an almost identical general pattern of innervation, with freely ending smooth or beaded nerve fibres emerging from dense nerve nets (fig. 7). Thicker portions of the whole mounts again revealed striated muscle fibres and motor end plates. The generally thinner periphery of the whole mounts presented the interesting appearance of small sheaves of terminal axons ending freely in discrete spots. In some of the preparations a sort of cross-sectional view of these spots revealed them to be "follicles" or "papillæ" with a rather thick "capsule" and a core containing the dot-like tips of terminal axons (fig. 8).

There appeared to be a striking resemblance between the nerve-nets of the rabbit's tongue and of the rabbit's skin and, to a certain extent, between the nerve endings of its lingual papillæ and of its hair-follicle, when viewed in the same plane.

Discussion

The three fundamental points that appear to emerge from this clinico-histological study are as follows: (1) An analysis of the gustatory acuity of different regions of the human tongue indicates that the zone of circumvallate papillæ and to a slightly lesser extent, the dorsum of the tip are gustatorily the most sensitive parts of the lingual mucosa. (2) An analysis of the nerve fibre density of different regions of the human tongue shows that the two above mentioned zones bear the most richly innervated papillæ and mucosa, the majority of fibres terminating freely and extragemmally. (3) Since, of these two regions, only the circumvallate papillary zone reveals an appreciable number of taste buds, a histoclinical correlation of maximal gustatory acuity and maximal nerve fibre density presents itself (Table III); at the same time areas with low papillary and neural density, such as the centre and sides of the anterior two-thirds of the tongue, manifested the poorest appreciation of sapid solutions. These observations call for a re-evaluation of the histological basis of gustation and of chemoreception, and for a renewal of emphasis on the role of the profusely innervated lingual epithelium.

The two hypotheses on the nature of gustatory sensibility that have been advanced in the last decade or so, also tend to minimize the importance of gustatory submodalities and of taste buds. Frings (1948) has contended that the four gustatory qualities—salty, sour, bitter and sweet—are merely familiar nodal points in a continuous taste spectrum, dependent on the stimulative capacity of electrolytes and non-electrolytes. Too much significance is not attached to the specificity of gustatory receptors, but to the *number* of them that are stimulated at any one time. This does not, however, make "taste different from all other senses" (Patton), because a fairly clear correlation between the number or density of the appropriate nerve fibres and the acuity of tactile or pain sense has now been established in the case of cutaneous sensibility (Dastur, 1955, and Weddell *et al.*, 1959). Recently Zotterman (1959) has mentioned that while pain could be evoked by pinching the mesenteric side of the bowel wall close to the site of entry of the innervating fibres, it could not be so evoked from the opposite side with its sparser nerve fibre density. Thus the observation embodied in the present study that the strength of the gustatory response appears linked to the richness of innervation of the lingual papilla merely fulfils expectations (*vide* Introduction).

The second and more soundly reared hypothesis, of Baradi and Bourne (1953), is based on the detection of certain sites of "enzyme activity" within and around taste buds and papillæ, and on the assumption that different sapid solutions variously disturb the base-line pattern of nerve impulses produced at these sites through ionic changes induced by this enzyme activity. More relevant here is the authors' observation that only a small proportion of the nerve fibres in the sub-epithelial plexus of the rabbit's papilla foliata passes into the taste buds, the majority extending into and around the epithelium of the gutters (resembling in some respects our present finding in the human tongue). Hence they suggest that a papilla with its buds and epithelium is a tasting unit, and that not only the buds themselves but the various adjacent parts of the epithelium contribute to the pattern of impulses which the brain interprets as a taste sensation.

The present investigation also provides some data on another controversial aspect of the problem of gustation, namely the localization of specific tastes over specific areas of the tongue, and the histological specificity or otherwise of the nerve fibres in these different regions. As shown in Table I, not only bitter but sweet and salty tastes also appear to be best mediated from the zone of circumvallate papillæ, when sapid solutions of comparable strengths were utilized. Similarly, although the quality of sourness was best evoked from the tip of the tongue, this fact seems less important than that all the 4 "primary" tastes were well appeciated over the tip. Histologically, too, there did not appear to be any difference between the nerve fibres or the pattern of innervation of various types of papillæ on different parts of the tongue. While a reduction in the density

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of nerve-mass was obvious, progressing from the circumvallate papilla and the fungiform papilla on the tip, to the epithelium on the undersurface of the tip (figs, 3, 2 and 5, respectively), to the mucosa on the mid-dorsum, pre-terminal smooth nerve fibres of comparable sizes and unencapsulated terminal axon filaments reaching up to the epithelium, were common to all parts of the tongue.

These observations would suggest very strongly that histologically different neural patterns or nerve fibres are not essential for transducing different types of taste sensations. This is reminiscent of the situation obtaining in other sensory localities, such as the hairy skin (Dastur, 1955, and Weddell *et al.*, 1955), the cornea (Lele and Weddell, 1956), and the angle of the anterior chamber of the eye (Holland *et al.*, 1956), where also freely ending axon filaments constitute the terminal neural ramifications and subserve a wide variety of sensory functions. It is becoming apparent that with gustation, as with these other "sensations," there are no real "modalities" or rigid specificities between structure and function at the level of the *terminal neural receptor*, which is probably concerned merely with reception and transduction of the sensory stimulus and not with its analysis or interpretation (which might well be attributes of the nerve fibres and of the CNS, respectively).

Only a few years ago, Moncrieff (1951) felt that the balance of evidence on the subject pointed to the existence of four different types of receptors specific to sour, salt, sweet and bitter, and to these receptors being connected through nerves and synapses. This cannot be considered too seriously in view of the recent histological evidence, such as that adduced in the present report, of a common and simple type of lingual neuroreceptor in human, rat and rabbit tongues (e.g. figs. 3 and 4). The gustatory receptor cells within the taste bud have now been made to shoulder the burden of a "chemical specificity" of taste (Pfaffmann, 1959), following upon studies (Kimura and Beidler, 1956) in which when ultramicroelectrodes were thrust into individual taste buds of the rat tongue, and the four basic taste stimuli were applied, a change in the resting potential was observed. There was little or no change when the electrode was in a region of the tongue lacking taste buds: this, however, one would expect if the electrode were away from the papillæ also, in sparsely innervated epithelium. This interesting observation also does not explain the retention of taste sensibility after taste-bud degeneration. Pfaffmann and Bare reported (Patton, 1950) that rats continue to distinguish between NaCl and H_2O after section of the chorda tympani (lingual) and glossopharyngeal nerves with complete degeneration of lingual taste buds. Patton and Richter (Patton, 1950) also failed to produce complete ageusia for quinine solutions by sectioning the lingual and glossopharyngeal nerves in rats.

To explain this, Patton suggested that the mediation of bitter and salty solutions in high concentrations might involve non-gustatory end organs.

But, in terms of the histology of nerve fibre endings at least, since there is no way of distinguishing between lingual receptors of common sensation and of gustation (present study), the observations of Pfaffmann and Bare and of Patton and Richter would suggest that the intact lingual epithelium, though totally denervated of gustatory nerves and only partially innervated by common sensory fibres is still capable of transducing certain strong taste stimuli. This, in turn, could only imply that extragemmal features play a role here, that the taste buds and the intragemmal nerve fibres are not absolutely specific or completely indispensable to gustation. In further support of this comes the recent report on gustatory preference-rejection tests on feral pigeons (Duncan, 1960), which were found to respond to a wide range of taste stimuli although histological examination did not reveal more than 50 to 60 taste buds in adult birds. The taste bud, then, might not be a *sine qua non* for gustation and chemoreception.

It would appear from the present investigation and discussion that the key-note of the neuro-histological basis of gustation and probably of other sensations, wherever situated, is simplicity with an essential uniformity, and, therefore, thinking in terms of the old concept of four discrete modalities of taste becomes redundant (also Baradi and Bourne).

Summary

A semi-quantitative evaluation of gustatory sensibility for the four main "tastes" was carried out over different areas of the tongue in 62 volunteer subjects. The zone of circumvallate papillæ was, gustatorily, the most sensitive area, the dorsum of the tip with its dense accumulation of fusiform papillæ being the next most sensitive area. The sides and the dorsum of the anterior two-thirds, both sparsely papillated, were much less sensitive on the whole. Sweet, salty and bitter tastes were all mediated best from the circumvallate zone, and sour best from the tip.

Histological examination of the lingual mucosa and submucosa, for connective tissues and nerve fibres (silver impregnation) was carried out on 26 tongues obtained at autopsy. Intrapapillary nerve fibres and subepithelial nerve bundles, were assessed semi-quantitatively, and were found to be most densely accumulated in the circumvallate zone and in the dorsum of the tip. The nerve fibres here, as well as in the less sparsely innervated regions of the sides, the centre and the posterior third of the tongue, were smooth axons which traversed the papillæ as coils or tufts and after terminal arborization, ended freely and singly among the epithelial cells. Methylene-blue-stained whole mounts of rat and rabbit tongue also revealed free nerve ends in the mucosa, and a pattern of nerve nets remarkably similar to that encountered in the skin.

Taste buds were encountered readily in the circumvallate papillæ, and only occasionally in the fungiform papillæ. Therefore a clear histoclinical correlation was evident only between the degree of acuity of gustation and

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the density of innervation of a given area. This situation was comparable to that obtaining in the skin and possibly in other parts of the body also. Thus the non-specifically but richly innervated lingual epithelium appeared to be the more significant histological substrate for transducing tastes.

Acknowledgments

I am indebted to Dr. V. R. Khanolkar, the Director, Indian Cancer Research Centre, for facilities provided. The comments and statistical advice of Dr. L. D. Sanghvi of the Indian Cancer Research Centre were invaluable. The bibliographic assistance of Dr. L. Guth of the National Institutes of Health (Bethesda, U.S.A.) is gratefully acknowledged. It is a pleasure to record the co-operation of Miss S. Kelkar, M.Sc., for the connective tissue stains, of Miss R. Ayengar, M.Sc., for the "Gros-Bielschowsky" preparations, and of Mr. P. B. Nath for the routine staining techniques. Thanks are also due to Mr. R. V. Nerurkar and Mr. A. V. Khopkar for photographic assistance. Finally, the clinical investigation would have been impossible without the willing collaboration of my colleagues of the Indian Cancer Research Centre during 1953 and 1955.

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PLATE LIII

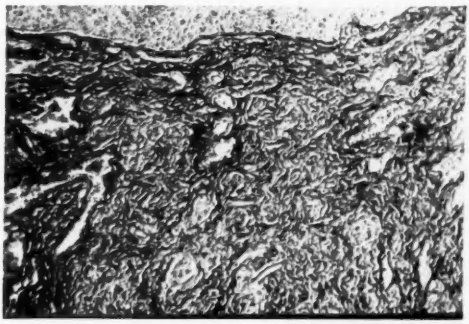

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

To illustrate article by Darab K. Dastur.

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FIG. 5.

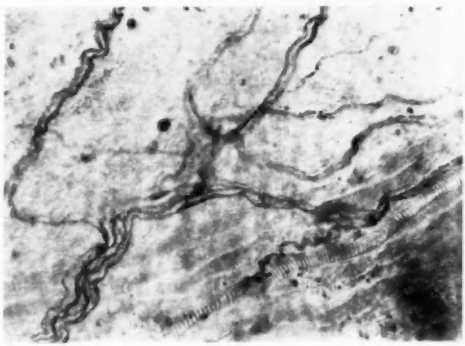

FIG. 6.

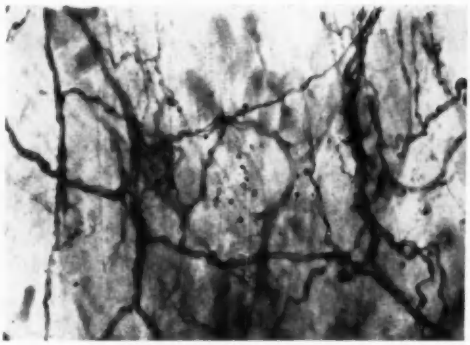

FIG. 7.

FIG. 8.

To illustrate article by Darab K. Dastur.

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LEGENDS TO PLATES

PLATE LIII

FIG. 1.—Vertical section through a circumvallate papilla showing connective tissue sheaths of fibres of a nerve tuft in the centre and darker collagenous tissue at the sides. (Masson's trichrome, ×-medium power.)

FIG. 2.—Frozen section through a fungiform papilla showing a complex tuft of nerve fibres with axon filaments terminating freely in and under the epithelium; deeper down a few filaments end in discs. (Gros-Bielschowsky, ×-high power.)

FIG. 3.—A transverse section (parallel to the surface) through a circumvallate papilla, showing dense innervation almost throughout and emphasizing the free axon terminals. (Gros-Bielschowsky, × 275.) Compare with fig. 1.

FIG. 4.—An unusually clear arborization of a papillary stem fibre into 5 terminal axon filaments which are ending freely. Two other branch filaments are seen to arise in the left lower quadrant, one from the same stem axon and one from its fellow. Also note the admixture of thick and thin fibres in the nerve coil towards the centre. (Gros-Bielschowsky, × 275.)

PLATE LIV

FIG. 5.—Epithelial protrusion on undersurface of tip of tongue. Note sparseness of innervation but "sameness" of nerve ending. (Holmes × 270.)

FIG. 6.—Mucosa of tip of rat tongue in methylene-blue-stained whole-mount, showing nerve net with branching twigs and filaments and a motor fibre ending with a motor end plate on a muscle fibre (lower half). (× 270.)

FIG. 7.—Methylene-blue-stained whole mount of mucosa on tip of rabbit tongue, showing a dense network of nerve twigs and fibres. Muscle fibres form the "background." (× 162.)

FIG. 8.—A "cross-sectional" view showing tips of terminal nerve filaments in the centre of follicular excrescences of the lingual epithelium of the rabbit. (Only a fraction of the fibres present can be in focus.) (× 270.)

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ON THE NATURE OF THE PIA MATER

BY

J. W. MILLEN AND D. H. M. WOOLLAM

(*From the Department of Anatomy, University of Cambridge*)

MOST current accounts of the pia mater describe it as a vascular membrane covering the spinal cord and the brain. Such descriptions have the merit of simplicity but are probably in part responsible for some of the misconceptions that have arisen in regard to the function of the pia mater and to the role of the blood vessels of the subarachnoid space in the production and absorption of the cerebrospinal fluid. Furthermore they are difficult to reconcile with the concept of perivascular spaces, lined by the pia mater, around the larger blood vessels which penetrate the central nervous system.

Key and Retzius (1875) divided the inner leptomeninx into the intima pia and the epipial tissue. They regarded the intima pia as a thin membrane which lay directly on the outer aspect of the nervous tissue. More superficially lay a meshwork of fibres containing blood vessels—the epipial tissue. The description of Key and Retzius though essentially accurate does not appear to have received any measure of general support.

The existence of capillaries on the surface of the central nervous system has often been denied (e.g. Flexner, 1933). Nevertheless physiological explanations of the manner of cerebrospinal fluid production and absorption depending on the presence of capillaries or capillary-like vessels in the subarachnoid space still have currency.

A re-examination of the pia mater has been made in an attempt to determine the relationships of the pia mater to the nervous tissue and in particular to the blood vessels which run in the subarachnoid space and enter the substance of the brain and spinal cord.

MATERIALS AND METHODS

Normal adult human spinal cords have been examined. Spinal cords from 69 mm. (3 months), 172 mm. (6 months) and 390 mm. (9 months) and stillborn fœtuses have also been investigated. Blocks have also been cut from adult human brains.

The material was routinely fixed in formol-acetic, Bouin's fixative and Bodian's fixative. Sections were prepared after paraffin embedding and treated with a variety of stains. The most valuable method was found to be Long's stain for reticulum

but sections were also stained with Mallory's trichrome, azan, Weigert's resorcin method, cresyl violet, Bodian's stain and hæmatoxylin and eosin.

Observations

In the adult human the spinal cord is closely invested by a thin continuous layer of reticular tissue (intima pia) (fig. 1). This reticular

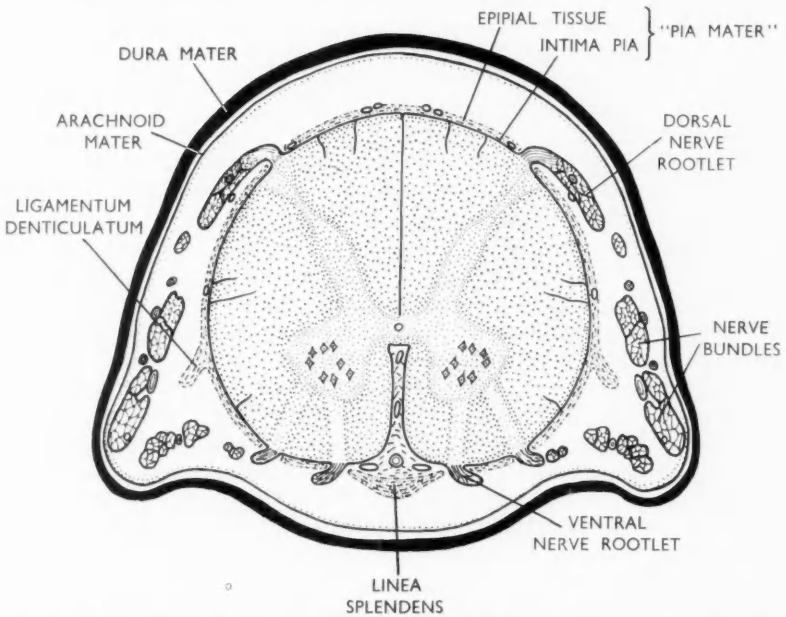

Fig. 1.—Diagram illustrating the relationships of the meninges to the spinal cord.

tissue follows the contours of the nervous tissue and passes down to the bottom of the anterior median fissure of the cord. It forms also the posterior median septum and the incomplete septa which project into the white matter at irregular intervals from the periphery of the cord. Where blood vessels enter or leave the cord the reticular layer dips in to form funnel-shaped depressions which are the mouths of the perivascular spaces. The reticular layer forms the outer lining of these spaces.

External to this reticular layer is a network of collagenous fibres (epipial tissue). This network is of fairly uniform thickness except at the sides of the cord and ventral to the anterior median fissure. On either side of the cord the collagenous layer is thickened and from it are formed the processes of the denticulate ligament which project laterally to be attached to the arachnoid and dura mater. The ventral thickening of

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this layer forms the linea splendens in front of the anterior spinal artery. The epipial layer of collagenous tissue also dips down into the depths of the anterior median fissure. It is interrupted and has blunt rounded margins where the nerve rootlets emerge from or enter the substance of the cord. The subarachnoid blood vessels lie among the strands of the epipial layer before entering the substance of the spinal cord. The deeper fibres of the epipial tissue often run circularly around the cord. The more superficial fibres are for the most part irregularly arranged; those forming the linea splendens have a mainly longitudinal direction. There are few trabeculæ to be seen crossing the subarachnoid space.

In the stillborn and 390 mm. fœtuses the arrangement of the spinal pia mater is similar to that in the adult. The reticular layer is well defined and has the same relationships as in the adult to the blood vessels and at the attachments of the nerve rootlets. There is a clearly marked epipial layer of collagenous tissue which forms the linea splendens and the ligamenta denticulata.

In the 172 mm. and 69 mm. fœtuses the reticular layer is readily revealed by the Long stain and its relationships are similar to those in the older fœtuses. On the other hand the epipial layer is very different in appearance. In the 172 mm. fœtus a very thin layer of epipial tissue can be detected over the surface of the cord and this layer forms also the processes of the ligamenta denticulata and a fairly well-defined linea splendens. In the 69 mm. fœtus the epipial collagenous tissue appears to be restricted to the ligamenta denticulata and a few fibres occupying the position of the linea splendens.

The brain is closely surrounded by a thin layer of reticular tissue. This intima pia covers the gyri and dips down to the depths of the sulci. A few fine septa pass into the cortex for a short distance but for the most part invaginations of the reticular tissue into the substance of the brain are associated with the entering or emerging blood vessels.

In contrast to the spinal cord there is no epipial layer of collagenous tissue over the cerebral hemispheres. An epipial layer is present on the medulla oblongata but the material examined did not reveal the upper limit of this layer. The blood vessels of the brain lie in the subarachnoid space and are loosely anchored to the pia and arachnoid by fine trabeculæ which appear from their staining to be reticular in nature. The smaller blood vessels lie directly in contact with the intima pia before entering the brain substance. Some reticular trabeculæ also cross the subarachnoid space between the pia and the arachnoid.

The Relationship of the Pia Mater to the Spinal Nerve Roots

Where the nerve filaments enter or emerge from the spinal cord the epipial tissue is interrupted and has blunt rounded margins. The reticular tissue of the pia mater proper, on the other hand, is pierced by

the individual nerve fibres and forms a sort of lamina cribrosa. Outside the cord each fibre carries a delicate investment of reticular tissue continuous with the intima pia and the whole filament is surrounded by a sheath of a similar nature. This outer sheath blends also with the pia mater on the surface of the cord.

As the filaments traverse the subarachnoid space they join together as large bundles and finally form the anterior and posterior nerve roots. These bundles and the nerve roots themselves carry a complete covering of reticular tissue so that the nerve fibres are always separated by a layer of reticular tissue from the cerebrospinal fluid in the subarachnoid space.

Where the nerve roots pierce the dura mater the outer covering of reticular tissue becomes continuous with the reticular tissue which forms the outer layer of the arachnoid mater. Distal to this the reticular covering of the individual fibres and bundles continues along the peripheral nerve and the whole nerve receives an outer sheath of collagenous fibres derived from the dura mater.

The Meningeal Relationships of the Blood Vessels in the Spinal Subarachnoid Space

The radicular vessels pierce the dura mater with or close to the nerve roots. Most of the larger vessels cross the subarachnoid space in association with the bundles of nerve fibres. Many smaller vessels are actually embedded among the nerve fibres which make up the bundles. In all these situations a distinct and complete investment of reticular tissue closely surrounds the wall of the blood vessels. This covering is continuous with the reticular tissue of the arachnoid mater. Upon reaching the spinal cord the branches of these vessels lie between the collagenous fibres of the epipial tissue but still retain their reticular covering which can be clearly differentiated from the surrounding collagenous fibres by its argyrophilia. The smaller vessels penetrate the substance of the spinal cord and the reticular sheath immediately surrounding each vessel forms the inner boundary of the perivascular space which accompanies the vessel into the cord. The outer wall of the space is formed by the dipping in of the pia mater proper on the surface of the cord. The epipial collagenous tissue takes no part in the formation of the perivascular sheaths.

No capillaries are present in the subarachnoid space and it is of importance that all the blood vessels in the subarachnoid space including those in the epipial tissue, even the most thin-walled veins, have a complete reticular layer separating them from the cerebrospinal fluid.

Discussion

Despite the description by Key and Retzius (1875) of an intima pia, immediately surrounding the nervous tissue, and a more superficial epipial

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layer, most accounts emphasize the vascular nature of the pia mater and regard it as a single homogeneous layer. From the observations described above it is clear that the description of Key and Retzius is more accurate. The true pia mater, the intima pia of Key and Retzius, is an argyrophilic membrane which closely invests the nervous tissue and ensheaths the nerves and blood vessels lying in the subarachnoid space. It is in continuity with the arachnoid membrane by reflections from the nerves and blood vessels where they pass through the arachnoid mater. This layer is completely avascular. In mammals, external to the true pia mater, there is an epipial layer composed of a loosely arranged network of collagenous fibres. This layer is particularly well marked along the lateral sides of the spinal cord where it forms the processes of the ligamenta denticulata and along the mouth of the anterior median fissure where it gives rise to the linea splendens. The epipial layer is relatively thick around the whole circumference of the adult human spinal cord and is also well marked in the full-term fœtal cord, but in embryos of 69 mm. and 172 mm. it is much less in amount and in the 69 mm. fœtus can only be identified in the region of the denticulate ligaments and at the linea splendens. No epipial layer can be recognized over the cerebral hemispheres. On the surface of the epipial layer and embedded among its fibres lie the blood vessels of the spinal cord before entering its substance. Over the cerebral hemispheres because of the absence of the epipial layer the blood vessels lie more distinctly in the subarachnoid space adjacent to the intima pia.

It has been frequently stated and is generally accepted that under normal functional conditions the leptomeninges, except for certain specialized parts, are relatively impermeable to the passage of fluids (Wislocki, 1928). This waterproofing quality as far as the pia mater is concerned must reside in the reticular layer, the true pia mater, since the interstices of the epipial collagenous tissue are permeated by the cerebrospinal fluid. Some current views on the formation and absorption of the cerebrospinal fluid would, however, exclude from this impermeability the blood vessels which lie in the subarachnoid space (Bowsher, 1957). Two points about these vessels are worthy of note. It was pointed out by Flexner (1933) and has been verified by many other workers that there are no capillaries in the subarachnoid space. In the second place all the blood vessels in the subarachnoid space are completely enclosed in a layer of reticular tissue derived from the arachnoid mater where they pierce it. This layer also surrounds the vessels as they lie in the epipial layer and forms the inner wall of the perivascular spaces around the entering and leaving blood vessels. The outer wall of the space is formed by an inflexion of the intima pia.

Although there is little or no information available about the permeability characteristics of reticular tissue it appears highly improbable

that the reticular layer surrounding the subarachnoid blood vessels does not partake of the same water-proofing qualities as the similar reticular layer bounding the subarachnoid space. Furthermore it is highly improbable that the blood vessels in the subarachnoid space should be unique in that, unlike the remainder of the body, vessels other than capillaries are permeable to the passage of fluids under normal physiological conditions. There is no unequivocal evidence for such transport.

The understanding of the structure of the pia mater is of fundamental importance to the solution of a further problem which has not as yet been satisfactorily answered, that of the development of the leptomeninges. Harvey and Burr (1926), from their transplantation experiments on amphibian embryos, put forward the view that the pia and arachnoid are derived wholly from the neural crest, a view which has received little support, and has been severely criticized by Flexner (1929) who regarded the meninges as entirely of mesodermal origin. The most recent account of the development of the meninges is that of Sensenig (1951). He concluded that ectodermal cells of neural crest origin mingle with the mesodermal cells so that the resultant pia mater has a dual origin. In human embryos of 10 to 20 somites Sensenig described a single layer of cells, apparently continuous with the neural crests, which extends ventrally along the lateral edges of the neural tube. He also traced the development of the processes of the denticulate ligaments as condensations of mesoderm extending from the lateral wall of the vertebral canal to the lateral walls of the neural tube. It seems not unreasonable to suggest that some of the disagreement has arisen from a failure to recognize the distinction between the pia mater proper, which bears an intimate relation to the nervous tissue, and the epipial layer which is directly continuous, by means of the processes of the denticulate ligaments, with the dura mater. A hypothesis which immediately suggests itself and is worthy of further examination, is that the intima pia is of neural crest origin whereas the epipial tissue, including the ligamenta denticulata, is of mesodermal origin.

Summary

(1) The pia mater has been studied in human adult and fœtal material with the aid of a stain for reticulum.

(2) The observations made bear out the description by Key and Retzius of an intima pia and a layer of epipial tissue. The intima pia, the true pia mater, is a layer of reticular tissue which surrounds the nervous tissue closely and invests the blood vessels and nerves lying in the subarachnoid space. The epipial tissue forms an additional layer of collagenous fibres superficial to the true pia mater. Among its meshes and on its outer surface lie the blood vessels of the subarachnoid space. This layer alone is concerned in the formation of the denticulate liga-

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ments and the linea splendens. It is not recognizable over the cerebral hemispheres.

(3) The absence of capillaries in the subarachnoid space and the isolation of the blood vessels from the cerebrospinal fluid by a reticular membrane identical with that which provides the impermeable lining of the subarachnoid space does not support theories of the formation and absorption of the cerebrospinal fluid which depend on the passage of fluids through the walls of these vessels.

(4) The dual nature of the pia mater and the arrangement of its two layers suggest the hypothesis that the intima pia is derived from the neural crest while the epipial tissue is of mesodermal origin.

ACKNOWLEDGMENTS

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NOTICES OF RECENT PUBLICATIONS

DISSEMINATED SCLEROSIS

Felduntersuchungen über Multiple Sklerose in Unterfranken: eine Studie an 110 *Patienten in* 46 *Gemeinden.* By HANS GEORG BAMMER. 1960. Pp. 103. Stuttgart: Georg Thieme Verlag. Price 15DM.

The serious attention this book merits may be simply stated: it comes from Würzburg and contains a foreword by Prof. G. Schaltenbrand. It gives results of the survey which has recently been completed by Dr. H. G. Bammer, on the prevalence and incidence of multiple sclerosis in Lower Franconia, and is directed especially to possible environmental factors in the ætiology of the disease.

For some years it has been known that a certain village ("Dorf F") in the Spessart district of the region had an unusual number of cases and, consequently, this was made the starting point of the survey. Altogether 46 communities (7 small towns and 39 villages) with a population of 79,396 were investigated. Some villages had only 250–312 inhabitants and in the towns populations ranged from 4–11,000, making an average for the 46 communities of 1,726 persons. Ascertainment of cases was through the local medical practitioners, examination of hospital records and death certificates, the period of review covering the years 1937–1956. All suspected patients were examined personally and steps were taken to exclude from prevalence calculations those not resident normally in the area. Prevalence day was fixed for January 1, 1958. A total of 153 patients was ascertained, but 25 of these were excluded because they showed insufficient evidence of multiple sclerosis and when the number had been pruned still further it fell to 91, a figure, however, which gave the high overall prevalence for the region of 115 cases per 100,000. The incidence between 1937 and 1956 was calculated to be 4·28 per 100,000 of the population.

It was found that the disease attacked both those who had lived all their lives in Lower Franconia and displaced persons or refugees, who had moved there in recent years. Indeed, between 1951 and 1952 the prevalence among refugees was higher than for the total population. The proportional relation of prevalence to town and country dwellers was 1 : 1·8, and the disease was noted to be particularly prevalent in communities where agriculture and forestry were the chief occupations, although no variation in incidence rates was found for the different occupations.

Dr. Bammer, in defining rural and urban dwellers, and being faced with so many small populations, found it best to ignore the actual size of these. He classified as "rural" those communities in which more than 30 per cent of the inhabitants derived

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their livelihood from farming, and "urban" those in which the proportion doing so was under that figure. He found no substantial difference as regards prevalence between places with bacteriologically clean drinking water and those with contaminated water supplies, but places having a high prevalence rate were often situated on tributary streams of the river Main and the dwellings of recently reported cases were found chiefly in the old parts of towns. Prevalence rate did not appear to be higher in communities where it was assumed there was a greater likelihood of inbreeding, and the incidence of familial and hereditary nervous diseases was probably higher among the families of indigenous patients than it was among refugee families. Among the inhabitants of the whole area only 9 patients were found who were (sometimes very distantly) related.

Perhaps the most interesting aspect of this work, however, is that in many of the communities studied patients were found living at the time of onset of their disease in close proximity to each other. Illustrations are given of adjacent dwellings and of houses in the same street occupied by patients. In these places there were primitive drainage arrangements for lavatories, waste, water, kitchen effluents, etc. Indeed only 5 of the 91 patients, during the ten years preceding onset of their illnesses, had been living in houses provided with satisfactory drains. Measurements were taken of the distances between houses in which patients with multiple sclerosis were known to have lived, both at the time of their birth and at the date of onset of the disease. It was found that whereas at birth only 47 per cent had lived within 200 metres of another patient, some 71 per cent at the time of onset were living within this range.

It is upon these observations that the author bases his conclusion, namely, that the observed examples of regionally circumscribed incidence point to the existence of some environmental factor in the causation of the disease. This is of great interest and more tangible, we think, than theories based on differing climatic conditions but one would have preferred to see the overall prevalence rate for Lower Franconia broken up and given in terms of sex and age-specific groups in relation to the population as a whole at risk. Differences in the age and sex structure of communities may, in part at least, influence both prevalence and incidence rates. In this survey the numbers of patients and the sizes of individual communities may be too small to make direct comparison of one village with another practicable. But the application of some such tests to provide a reliable denominator would enhance the work, the value of which cannot be in doubt. The data provided on the proximity of patients' dwellings might be interpreted as meaning that where population density per unit of linear measurement is increased, the probability of contact with a local environmental factor is increased, but on p. 52, fig. 41, the ordinate might better be represented by a *rate* rather than by the actual number of patients.

The methods employed in ascertainment of the clinical material are commendably thorough, especially the care taken to supplement histories with the aid of relatives. The author has taken the trouble to provide in the appendix to his book careful summaries of the case records and these leave no doubt as to the validity of the diagnosis in all accepted cases.

R. S. ALLISON.

Multiple Sclerosis: Prognosis and Treatment. By LEO ALEXANDER, M.D., AUSTIN BERKELEY, Ph.D., and ALENE ALEXANDER. 1961. Pp. 188. Oxford: Blackwell. Price 60s.

The statistical analysis of clinical phenomena is a method of investigation only recently developed, but it is one which holds considerable promise, especially in

dealing with the difficult problems of evaluation of therapy. During the past ten years Dr. Leo Alexander of the Boston State Hospital has used a method based on the numerical scoring of disability to clarify the patterns of natural history of multiple sclerosis, as a guide in prognosis, and to try and assess the effects of a variety of treatments. One can hardly imagine a more difficult field for the application of this method or one where it is more urgently required. Dr. Alexander's laborious studies are described in a book which will intrigue every physician interested in this disease and will doubtless encourage others to follow up his methods of measurement in this confused field.

Dr. Alexander furnishes convincing evidence of the value of ACTH in the treatment of acute cases of multiple sclerosis: it is difficult to envisage any convincing theoretical reason for the allegedly inferior results obtained with Prednisone. He also attempts a statistical evaluation of the effects of treatment with repeated small blood transfusions in more chronic cases, and especially in those where there has been poor recovery from an acute attack. This is a method of treatment little employed in Great Britain but extensively used in Germany where it has some distinguished adherents. The new evidence adduced by Dr. Alexander is suggestive, and indicates that this method of treatment merits further observations here. Its rationale is obscure and it has been justified on grounds as various as that it furnishes a fresh supply of antibodies of some kind or that it "fills the vascular tree." Neither of these explanations nor any of the others so far offered carry much conviction, but there are after all many forms of treatment which have been shown to be valuable long before their theoretical basis was understood.

The amount of statistical analysis to which Dr. Alexander's clinical material is subjected sometimes gives the impression that his study is rather top-heavy, and raises doubts as to the validity of fine distinctions based entirely on statistical findings, but the work is a bold and pioneer venture in a forbidding field, and comprises the most stimulating clinical study of this disease published during recent years.

HENRY MILLER.

CEREBRAL PALSY

Speech Therapy in Cerebral Palsy. By MERLIN J. MECHAM, Ph.D., MARTIN J. BERKO, M.A., and FRANCES GIDEN BERKO, M.A. 1961. Pp. 307. Oxford: Blackwell. Price £4.

Speech therapists and other medical auxiliaries must know something about cerebral palsy, and this book is intended for them. None of the authors is medically qualified which may explain the use of words like "aphasoid" and statements like "we may classify stuttering together with tics as striate body neurosis." Each chapter has a summary and bibliography but the literature is not critically reviewed. There are useful appendices, including a table giving the stages of normal verbal language development. Though it is disappointing to us to read that Dr. Little was "an English orthopædist" this book may with reticence be recommended.

Stuttering and What You Can Do About It. By WENDELL JOHNSON. 1961. Pp. 208. Oxford University Press. Price 32s.

This book is intended for stutterers and their relatives and is written by a recovered stutterer. It is well produced and is accurate for the author is Head of the well-known unit of Speech Pathology at the University of Iowa and has contributed much to the literature of this subject.

F. CLIFFORD ROSE.

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The Pathology of Cerebral Palsy. By ABRAHAM TOWBIN, M.D. 1960. Pp. 206. Oxford: Blackwell. Price 64s.

Evaluation and Management of the Brain-Damaged Patient. By JEROME S. TOBIS, M.D., and MILTON LOWENTHAL, M.D. 1960. Pp. 109. Oxford: Blackwell. Price 48s.

The Tutoring of Brain-Injured Mentally Retarded Children. By JAMES J. GALLAGHER, Ph.D. 1960. Pp. 194. Oxford: Blackwell. Price 54s.

Dr. Towbin's book describes and illustrates the many pathological conditions which can be found in cases of cerebral palsy, but although it sets out to correlate pathology with clinical findings, it leaves the impression that almost any pathological condition can have almost any clinical manifestation. This is admittedly not the fault of the author, for in this field correlation between accurate clinical findings and pathology is exceptional. As usual, all the cases described (very briefly) are severely affected physically and also mentally defective; one searches in vain for the pathology of minimal diplegia. The author's contention that anoxia is the root cause of nearly all the pathological changes described may be popular at present though it is not by any means proved, and his distinction between the results of brain disease in early and late embryonic life is not sufficiently clear. Furthermore the pathological descriptions are mostly confined to the cortex and relatively little attention is given to the basal ganglia and the brain stem. The unpleasant fact remains that cerebral palsy doesn't make sense, and this book does little to make sense of it; in all fairness it must be admitted that this failure to clarify a subject of great complexity should be laid at the door of the clinician rather than of the pathologist. 64s., however, is a lot to pay for a feeling of dissatisfaction.

Dr. Tobis and Dr. Lowenthal's book is a popular exposition of the principles of physical medicine as applied to neurological patients. Dr. Gallagher's "The Tutoring of Brain-Injured Mentally Retarded Children" is a more serious study of the effect of individual tuition on imbecile children whose retardation was considered to be due to brain damage. He found that tuition is more effective in the younger child and that it results in a greater increase in verbal ability than in performance and conceptualization. He also remarks that the concept of "brain damage" is of no particular value to the teacher: what the teacher does have to know is the pattern of intellectual development and the behavioural difficulties of the particular child. Disturbing though this may be to the neurologist, it is probably true at the present state of our knowledge of the education of the mentally subnormal.

JOHN FOLEY.

CHILD DEVELOPMENT

Handbook of Research Methods in Child Development. Ed. P. H. MUSSEN. 1960. Pp. 1061. London: John Wiley & Sons. Price 122s.

All that Shakespeare wrote in Hamlet is doubtless also contained in any standard English dictionary. Yet no one would question which is the more difficult to read. This volume resembles the dictionary, or as its preface states, a catalogue—"a handbook to make available in a single source concrete descriptions and evaluations of the most widely used research techniques in many aspects of the study of child growth and behaviour." Thus, even with a thousand odd pages, it makes no claim to be comprehensive. (And a strong pair of hands is needed. Ought any book to be quite so heavy. The type, paper and format, with a divided page, make it a joy to read but not to handle).

With a variety of contributors, and wide coverage, some repetition is inevitable; this increases both its value and readability, and an excellent index simplifies the cross referencing. Occasionally a chapter seems to extol research methods as such, and in the process, to lose sight of the object to be achieved. In a chapter on research methods in children's learning we read that research programmes "are bringing laboratory methods to the teaching of academic content. They have devised apparatus —teaching machines—that permits the administration of carefully prepared teaching programs to the learner." We had thought once upon a time that the function of education was to draw out rather than to pump in. Here and there new jargon creeps in, and again it seems to be the fault of the machines. "A general growth of interest in instrumentation, stemming from the rise of logical positivism, with its attendant stress upon operationalism, has also encouraged the development of techniques in all spheres, including the projective." This is, of course, an American text and the references contain much work that is little known in this country. What is invaluable is that here one has the opportunity of reading much of what has already been attempted, as well as how and why, in the field of child development. Due place is given to the more theoretical, even philosophical aspects, and the chapter (16) on "Children's attitudes and values" is an excellent example of a most interesting essay on a highly complex subject. Throughout the book light is thrown on accepted concepts such as a child's likely reaction to any interview from a stranger, stimulating both a critical study of one's own methods, and the means of easily comparing our own with others.

We must be grateful for the industry and scholarship that make this a major, indeed an invaluable, book.

E. M. CREAK.

CHOLINESTERASE

Histochemistry of Cholinesterase. Bibliotheca Anatomica Fasc. 2. Ed. H. G. SCHWARZACHER. Pp. 255. Basel: S. Karger. S. Fr. 60.

The role of acetylcholine as transmitter substance in both the central and peripheral nervous system is so much better defined than that of any of the more recently identified transmitter substances that it is bound to occupy the attention of physiologically minded neurologists more than any other single chemical compound. Unfortunately its presence and location cannot be easily demonstrated. This disadvantage is not shared by the enzyme for which acetylcholine is the substrate—acetylcholinesterase, so that the presence of this enzyme is the most easily obtained indication of the site of liberation. A number of methods have been developed for the histochemical demonstration of acetylcholinesterase and our knowledge of its location both within and outside the nervous system has received important contribution in recent years. The book here reviewed is concerned with these contributions. It takes the form of a supplement to Acta Anatomica and contains 24 papers most of them being refreshingly short reviews of work previously carried out by the authors on the particular aspect of acetyl cholinesterase which has interested them. Four of the papers are concerned with technique and it is interesting to note already a second technique for demonstration of cholinesterase in electron microscope preparations. Particularly impressive is the demonstration by Shute and Lewis of the participation of acetyl cholinesterase in the axonic flow. Snell's study of the topography of cholinesterase activity will be particularly satisfying to those seeking to inject functional significance into their histological preparations. To mention only one striking example, Snell was able to demonstrate quite dramatically the marked contrast in

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cholinesterase activity in the anterior and posterior spinal roots. The presence of cholinesterase activity in some sensory receptors in the skin described in this volume by Canna is an indication of the economy of nature in using a single substance in the indication of both motor and sensory function.

It is also most pleasing to find in these collected papers contributions by those pioneer investigators of the histochemistry of the myoneural junction, Professor Couteaux, Dr. Coërs and the editor himself. The former brings to our notice the existence of a remarkable junction in the sea horse (hippocampus) in which the cholinesterase appears to be confined to a presynaptic site within the axonic terminals. One further paper requires special mention. This is the demonstration by Waser and Hardorn from Zürich of the location of curarine in normal and denervated muscle with an autoradiographic technique using ^{14}C-curarine. Space does not permit mention of the other papers which cover embyrological and comparative anatomical aspects and the presence of cholinesterase in non-nervous tissue.

There is no doubt that this book contains much of interest to those working in the field, though it is only right to point out that this is one of the growing points of neurology and the supplement, excellently produced though it is, is bound to have a limited life as a reference work.

A. L. WOOLF.

GENERAL NEUROLOGY

Scientific Aspects of Neurology. Leeds Neurological Sciencies Colloquium 1959–60. Ed. HUGH GARLAND. 1961. Pp. 264. London: E. & S. Livingstone. Price 50s.

Dr. Garland has edited an admirably produced volume containing 20 post-graduate lectures in the neurological sciences. The first is by Sir Francis Walshe on the origin of the pyramidal tract; the last is on the rational use of tranquillizing drugs by Dr. J. M. Roberts, the University of Leeds Lecturer in Psychiatry. In between we find contributions by a remarkable group of eminent men, each speaking on his own subject, usually a life-long study.

It is encouraging to find three papers, of a positive if still groping nature, concerned with the urgent problems of demyelinating disease, by Dr. van Bogaert, Dr. Miller and Professor Lumsden: and that broad matters such as sleep (the late Sir Geoffrey Jefferson) and asymmetry of cerebral hemisphere function (Professor Zangwill) also hold their own against perhaps simpler clinico-physiological matters.

While it is impossible to give any detailed review of 20 very dissimilar papers here, it is certainly possible to recommend the book to anyone concerned to know what matters are considered fundamental to neurology in the middle of the twentieth century. At a point when it is difficult to see the correct orientation points for neurology, one cannot say how much of the work incorporated in this book will prove enduring. Each author has taken his subject to the very limits of modern knowledge about it: and the student, either very senior or very junior, should feel enjoyment and enlightenment in making contact with what many of our best men really feel about their subject.

WILLIAM GOODDY.

Essentials of Neurology. By JOHN N. WALTON. 1961. Pp. 422. London: Pitmans. Price 30s.

"The intention has been to make this a book which can be read by the student who wishes to obtain a composite picture of neurological illness, but can also be used for

reference if need be," writes Dr. Walton. The student will be glad to have so much clearly stated neurology for so little, and further references in the form of half a dozen well-chosen works at each chapter-end. The first two hundred pages are concerned with the basis of clinical neurology, and its application to the patient, the rest with the description of disease. It is all done clearly and simply, nominal milestones within the text having heavy type. There are no illustrations and tables and few diagrams, but the text is cursive and not fatiguing. Details of management and of treatment will give the student a humane introduction to neurology, and as Dr. Walton also includes scholarly comments upon rare disorders the "Essentials of Neurology" will give him a healthy respect for the subject as a whole.

It was ambitious to write yet another textbook of neurology, but the work justifies itself.

DENIS WILLIAMS.

Kernicterus and Its Importance in Cerebral Palsy. Pp. 306. Oxford: Blackwell. Price 70s.

This book is the verbatim report of a meeting of the American Academy of Cerebral Palsy in 1957 which was devoted to Kernicterus. The most important section is an extensive account of the pathology of this condition, based on 87 cases, which was contributed by a group of neuro-pathologists headed by Dr. Webb Haymaker. Other interesting contributions relate to clinical and experimental observations on hyperbilirubinæmia.

J. PURDON MARTIN.

Atlas for Stereotaxic Brain Research on the Conscious Rabbit. By M. MONNIER and H. GANGLOFF. 1961. Pp. 76. Amsterdam: Elsevier Publishing Company. Price 63s.

This volume is designed for use with the Monnier and Gangloff stereotaxic equipment developed for the conscious rabbit. Over half the pages are concerned with physiological technique and experimental research in the field of neuropharmacology. The anatomical section is confined to three outline drawings of sagittal sections and seven drawings of frontal sections. No quantitative data on the anatomical variability between different animals are given. The text is in English, French and German and the book is well produced.

J. A. V. BATES.

SHORTER NOTICES

Evaluation of Drug Therapy. Ed. FRANCIS M. FORSTER, M.D. 1961. Pp. 165. University of Wisconsin Press. Price 4 dollars.

A meeting was held to try to agree standards upon which the efficacy of neurological treatment could be judged. After discussion of the pharmacological and procedural problems of clinical trials, special disorders were considered; these were epilepsy, vertigo, the neuropathies, headache, glaucoma, multiple sclerosis, and diseases of muscles and of the basal ganglia. The little book constitutes the minutes.

The Surgical Treatment of Intracranial Meningiomas. By C. S. MACCARTY, M.D. 1961. Pp. 69. Oxford: Blackwell. Price 36s.

This is a slim brochure of approaches to meningiomas, prettily illustrated. Those who remove meningiomas will not need it, whilst those who need it should not try to do so.

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Motor Examination of Peripheral Nerve Injuries. By Y. T. Oester, M.D., and J. H. Mayer, M.D. 1961. Pp. 89. Oxford: Blackwell. Price 44s.

The little book is an illustrated account of how to recognize the motor and sensory effects of nerve injury, by bedside examination. It is twenty times as expensive as the Medical Research Council's "Aids to the Investigation of Peripheral Nerve Injuries," which covers the same ground, and is still available at the Stationery Office.

Cysticercosis: An Analysis and Follow-up of 450 *Cases.* By H. B. F. Dixon and F. M. Lipscomb. 1961. Medical Research Council Special Report Series No. 299. Pp. 56. London: Her Majesty's Stationery Office. Price 6s. 6d.

This follow-up study is a continuation of the original research on cysticercosis begun by Sir William Mac Arthur in 1929. It investigates amongst other things the incidence, incubation period, symptomatology and prognosis of cysticercosis in the individuals exposed to the risk of infection in the British Army in India. It is a useful factual survey. There is an error in the heading of Table 4 which gives the figures of calcification of cysticerci within the skull and not as stated in skeletal muscles.